Nucleic Acids, Proteins and Antibodies

[0001] This application is a claims benefit of priority under 35 U.S.C. § 365(c) and § 120 to International Application Number PCT/US00/05988, filed March 8, 2000 which was published by the International Bureau in the English language as International Publication Number WO/0055174 on September 21, 2000 and under 35 U.S.C. § 119(e) to U.S. Application No. 60/124,270 filed March 12, 1999, both of which are hereby incorporated by reference herein.

Statement under 37 C.F.R. § 1.77(b)(4)

[0002] This application refers to a "Sequence Listing" listed below, which is provided as an electronic document on two identical compact discs (CD-R), labeled "Copy 1" and "Copy 2." These compact discs each contain the following files, which are hereby incorporated in their entirety herein:

Document	File Name	Size in bytes	Date of Creation
Sequence Listing	PA101SEQLIST.txt	3,111,160	08/07/2001

Field of the Invention

[0003] This invention relates to newly identified prostate or prostate cancer related polynucleotides, the polypeptides encoded by these polynucleotides herein collectively referred to as "prostate cancer antigens," and to the complete gene sequences associated therewith and to the expression products thereof, and to antibodies that immunospecifically bind these polypeptides, as well as the use of such prostate cancer polynucleotides, antigens, and antibodies for detection, prevention, prognosis, and treatment of disorders of the reproductive system, particularly disorders of the prostate, including, but not limited to, the presence of prostate cancer and prostate cancer metastases. More specifically, isolated prostate cancer nucleic acid molecules are provided encoding novel prostate cancer polypeptides. Novel prostate cancer polypeptides and antibodies that bind to these polypeptides are provided. Also provided are vectors, host cells, and recombinant and synthetic methods for producing human prostate cancer polynucleotides, polypeptides, and/or antibodies. The invention further relates to diagnostic and therapeutic methods useful for diagnosing, treating, preventing and/or prognosing disorders related to the prostate, including prostate cancer, and therapeutic methods for treating such disorders. The invention further relates to screening methods for identifying agonists and antagonists of polynucleotides and polypeptides of the invention. The invention further relates to methods and/or compositions for inhibiting or promoting the production and/or function of the polypeptides of the invention.

Background of the Invention

[0004] The normal prostate gland is quite small, weighing only about one ounce, and comprised of approximately 30% muscular tissue and 70% glandular tissue. The prostate wraps around the urethra, through which urine and semen are carried out to the tip of the penis. The primary function of the prostate is to produce a necessary fluid component of semen; just prior to male orgasm muscular contractions squeeze this fluid into the urethra. Disorders of the prostate gland, such as prostate cancers, are typically manifested by enlargement of the gland, leading to such symptoms as impaired urinary flow, infertility, and pain.

[0005] About 180,000 new cases of prostate cancer in the United States and 16,000 in Canada are diagnosed every year. Cancer of the prostate is now the second most common type of cancer in males, although the causes of prostate cancer are not well understood. While men of any age can develop prostate cancer, it is found most frequently in men over age 50, with risk increasing with age.

[0006] Most prostate cancers are adenocarcinomas, cancers that arise in glandular cells of the prostate's epithelial tissue. Types of prostate cancers also include, but are not limited to, transitional cell carcinomas, ductal carcinomas, and squamous cell carcinomas. Prostate cancers usually progress slowly and produce no symptoms in the initial stages. Eventually, the tumor may enlarge the prostate gland, pressing on the urethra and causing painful or frequent urination and blood in the urine or semen. Sometimes pain in the lower back, pelvis, or upper thighs may signal that prostate cancer cells have spread to the ribs, pelvis, and other bones. The prognosis for prostate cancer is quite good if it is caught and treated early. The five-year survival rate for American men with prostate cancer is almost 93 percent, but this number rises to almost 100 percent if the tumor is caught early.

[0007] Current therapies include watchful waiting, surgery, radiation therapy, and hormone therapy, which may lead to such unpleasant side effects as incontinence, impotence, dry orgasm, pubic hair loss, nausea, breast growth, and decreased libido.

[0008] There are a variety of techniques for early detection and characteristics of prostate cancers, however, none of them are devoid of problems. Because prostate cancer is a notoriously silent disease with few early symptoms, there is an urgent need for identification and characterization of factors that modulate activation and differentiation of prostate cells, both normally and in disease states. In particular, there is a need to isolate and characterize additional molecules that mediate apoptosis, DNA repair, tumor-mediated angiogenesis, genetic imprinting, immune responses to tumors and tumor antigens, among other things, that can play a role in detecting, preventing, ameliorating or correcting dysfunctions or diseases related to the prostate.

[0009] The discovery of new human prostate cancer associated polynucleotides, the polypeptides encoded by them, and antibodies that immunospecifically bind these polypeptides, satisfies a need in the art by providing new compositions which are useful in the diagnosis, treatment, prevention and/or prognosis of disorders of the reproductive system, particularly disorders of the prostate, including, but not limited to, prostate cancers

such as adenocarcinoma, transitional cell carcinomas, ductal carcinomas, and squamous cell carcinomas, as well as inflammatory disorders, such as chronic prostatitis, granulomatous prostatitis and malacoplakia, prostatic hyperplasia, and as described under "Hyperproliferative Disorders" and/or "Reproductive System Disorders" below.

Summary of the Invention

[0010] The present invention includes isolated nucleic acid molecules comprising, or alternatively, consisting of, a prostate and/or prostate cancer associated polynucleotide sequence disclosed in the sequence listing (as SEQ ID Nos:1 to 940) and/or contained in a human cDNA clone described in Tables 1, 2 and 5 and deposited with the American Type Culture Collection ("ATCC"). Fragments, variant, and derivatives of these nucleic acid molecules are also encompassed by the invention. The present invention also includes isolated nucleic acid molecules comprising, or alternatively consisting of, a polynucleotide encoding a prostate or prostate cancer polypeptide. The present invention further includes prostate and/or prostate cancer polypeptides encoded by these polynucleotides. Further provided for are amino acid sequences comprising, or alternatively consisting of, prostate and/or prostate cancer polypeptides as disclosed in the sequence listing (as SEQ ID Nos: 941 to 1880) and/or encoded by a human cDNA clone described in Tables 1, 2 and 5 and deposited with the ATCC. Antibodies that bind these polypeptides are also encompassed by the invention. Polypeptide fragments, variants, and derivatives of these amino acid sequences are also encompassed by the invention, as are polynucleotides encoding these polypeptides and antibodies that bind these polypeptides. Also provided are diagnostic methods for diagnosing and treating, preventing, and/or prognosing disorders related to the prostate, including prostate cancer, and therapeutic methods for treating such disorders. The invention further relates to screening methods for identifying agonists and antagonists of prostate cancer antigens of the invention.

Detailed Description

<u>Tables</u>

[0011] Table 1 summarizes some of the prostate cancer antigens encompassed by the invention (including contig sequences (SEQ ID NO:X) and the cDNA clone related to the contig sequence) and further summarizes certain characteristics of the prostate cancer polynucleotides and the polypeptides encoded thereby. The first column shows the "SEQ ID NO:" for each of the 940 prostate cancer antigen polynucleotide sequences of the invention. The second column provides a unique "Sequence/Contig ID" identification for each prostate and/or prostate cancer associated sequence. The third column, "Gene Name," and the fourth column, "Overlap," provide a putative identification of the gene based on the sequence similarity of its translation product to an amino acid sequence found in a publicly accessible gene database and the database accession no. for the database sequence having similarity, respectively. The fifth and sixth columns provide the location (nucleotide position nos. within the contig), "Start" and "End", in the polynucleotide sequence "SEQ ID NO:X" that delineate the preferred ORF shown in the sequence listing as SEQ ID NO:Y. The seventh and eighth columns provide the "% Id" (percent identity) and "% Si" (percent similarity), respectively, observed between the aligned sequence segments of the translation product of SEQ ID NO:X and the database sequence. The ninth column provides a unique "Clone ID" for a cDNA clone related to each contig sequence.

[0012] Table 2 summarizes ATCC Deposits, Deposit dates, and ATCC designation numbers of deposits made with the ATCC in connection with the present application.

[0013] Table 3 indicates public ESTs, of which at least one, two, three, four, five, ten, fifteen or more of any one or more of these public EST sequences are optionally excluded from certain embodiments of the invention.

[0014] Table 4 lists residues comprising antigenic epitopes of antigenic epitope-bearing fragments present in most of the prostate or prostate cancer associated polynucleotides described in Table 1 as predicted by the inventors using the algorithm of Jameson and Wolf, (1988) Comp. Appl. Biosci. 4:181-186. The Jameson-Wolf antigenic analysis was performed using the computer program PROTEAN (Version 3.11 for the Power MacIntosh, DNASTAR, Inc., 1228 South Park Street Madison, WI). Prostate and prostate cancer associated polypeptides (e.g., SEQ ID NO:Y, polypeptides encoded by SEQ ID NO:X, or polypeptides encoded by the cDNA in the referenced cDNA clone) may possess one or more antigenic epitopes comprising residues described in Table 4. It will

be appreciated that depending on the analytical criteria used to predict antigenic determinants, the exact address of the determinant may vary slightly. The residues and locations shown in column two of Table 4 correspond to the amino acid sequences for most prostate and prostate cancer associated polypeptide sequence shown in the Sequence Listing.

[0015] Table 5 shows the cDNA libraries sequenced, and ATCC designation numbers and vector information relating to these cDNA libraries.

Definitions

[0016] The following definitions are provided to facilitate understanding of certain terms used throughout this specification.

[0017] In the present invention, "isolated" refers to material removed from its original environment (e.g., the natural environment if it is naturally occurring), and thus is altered "by the hand of man" from its natural state. For example, an isolated polynucleotide could be part of a vector or a composition of matter, or could be contained within a cell, and still be "isolated" because that vector, composition of matter, or particular cell is not the original environment of the polynucleotide. The term "isolated" does not refer to genomic or cDNA libraries, whole cell total or mRNA preparations, genomic DNA preparations (including those separated by electrophoresis and transferred onto blots), sheared whole cell genomic DNA preparations or other compositions where the art demonstrates no distinguishing features of the polynucleotide/sequences of the present invention.

[0018] As used herein, a "polynucleotide" refers to a molecule having a nucleic acid sequence contained in SEQ ID NO:X (as described in column 1 of Table 1) or the related cDNA clone (as described in column 9 of Table 1 and contained within a library deposited with the ATCC). For example, the polynucleotide can contain the nucleotide sequence of the full length cDNA sequence, including the 5' and 3' untranslated sequences, the coding region, as well as fragments, epitopes, domains, and variants of the nucleic acid sequence. Moreover, as used herein, a "polypeptide" refers to a molecule having an amino acid sequence encoded by a polynucleotide of the invention as broadly defined (obviously

excluding poly-Phenylalanine or poly-Lysine peptide sequences which result from translation of a polyA tail of a sequence corresponding to a cDNA).

[0019] In the present invention, "SEQ ID NO:X" was often generated by overlapping sequences contained in multiple clones (contig analysis). A representative clone containing all or most of the sequence for SEQ ID NO:X is deposited at Human Genome Sciences, Inc. (HGS) in a catalogued and archived library. As shown in column 9 of Table 1, each clone is identified by a cDNA Clone ID. Each Clone ID is unique to an individual clone and the Clone ID is all the information needed to retrieve a given clone from the HGS library. In addition to the individual cDNA clone deposits, most of the cDNA libraries from which the clones were derived were deposited at the American Type Culture Collection (hereinafter "ATCC"). Table 5 provides a list of the deposited cDNA libraries. One can use the Clone ID to determine the library source by reference to Tables 2 and 5. Table 5 lists the deposited cDNA libraries by name and links each library to an ATCC Deposit. Library names contain four characters, for example, "HTWE." The name of a cDNA clone ("Clone ID") isolated from that library begins with the same four characters, for example "HTWEP07". As mentioned below, Table 1 correlates the Clone ID names with SEQ ID NOs. Thus, starting with a SEQ ID NO, one can use Tables 1, 2 and 5 to determine the corresponding Clone ID, from which library it came and in which ATCC deposit the library is contained. Furthermore, it is possible to retrieve a given cDNA clone from the source library by techniques known in the art and described elsewhere herein. The ATCC is located at 10801 University Boulevard, Manassas, Virginia 20110-2209, USA. The ATCC deposits were made persuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for the purposes of patent procedure.

[0020] A "polynucleotide" of the present invention also includes those polynucleotides capable of hybridizing, under stringent hybridization conditions, to sequences contained in SEQ ID NO:X, or the complement thereof (e.g., the complement of any one, two, three, four, or more of the polynucleotide fragments described herein), and/or sequences contained in the related cDNA clone within a library deposited with the ATCC. "Stringent hybridization conditions" refers to an overnight incubation at 42 degree C in a solution comprising 50% formamide, 5x SSC (750 mM NaCl, 75 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate,

and 20 μg/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1x SSC at about 65 degree C.

[0021] Also included within "polynucleotides" of the present invention are nucleic acid molecules that hybridize to the polynucleotides of the present invention at lower stringency hybridization conditions. Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide concentration (lower percentages of formamide result in lowered stringency); salt conditions, or temperature. For example, lower stringency conditions include an overnight incubation at 37 degree C in a solution comprising 6X SSPE (20X SSPE = 3M NaCl; 0.2M NaH_2PO_4; 0.02M EDTA, pH 7.4), 0.5% SDS, 30% formamide, 100 ug/ml salmon sperm blocking DNA; followed by washes at 50 degree C with 1XSSPE, 0.1% SDS. In addition, to achieve even lower stringency, washes performed following stringent hybridization can be done at higher salt concentrations (e.g. 5X SSC).

[0022] Note that variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress background in hybridization experiments. Typical blocking reagents include Denhardt's reagent, BLOTTO, heparin, denatured salmon sperm DNA, and commercially available proprietary formulations. The inclusion of specific blocking reagents may require modification of the hybridization conditions described above, due to problems with compatibility.

[0023] Of course, a polynucleotide which hybridizes only to polyA+ sequences (such as any 3' terminal polyA+ tract of a cDNA shown in the sequence listing), or to a complementary stretch of T (or U) residues, would not be included in the definition of "polynucleotide," since such a polynucleotide would hybridize to any nucleic acid molecule containing a poly (A) stretch or the complement thereof (e.g., practically any double-stranded cDNA clone generated using oligo dT as a primer).

[0024] The polynucleotides of the present invention can be composed of any polyribonucleotide or polydeoxribonucleotide, which may be unmodified RNA or DNA or modified RNA or DNA. For example, polynucleotides can be composed of single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or,

more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, the polynucleotide can be composed of triple-stranded regions comprising RNA or DNA or both RNA and DNA. A polynucleotide may also contain one or more modified bases or DNA or RNA backbones modified for stability or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications can be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically, or metabolically modified forms.

[0025] In specific embodiments, the polynucleotides of the invention are at least 15, at least 30, at least 50, at least 100, at least 125, at least 500, or at least 1000 continuous nucleotides but are less than or equal to 300 kb, 200 kb, 100 kb, 50 kb, 15 kb, 10 kb, 7.5kb, 5 kb, 2.5 kb, 2.0 kb, or 1 kb, in length. In a further embodiment, polynucleotides of the invention comprise a portion of the coding sequences, as disclosed herein, but do not comprise all or a portion of any intron. In another embodiment, the polynucleotides comprising coding sequences do not contain coding sequences of a genomic flanking gene (i.e., 5' or 3' to the gene of interest in the genome). In other embodiments, the polynucleotides of the invention do not contain the coding sequence of more than 1000, 500, 250, 100, 50, 25, 20, 15, 10, 5, 4, 3, 2, or 1 genomic flanking gene(s).

[0026] "SEQ ID NO:X" refers to a prostate cancer antigen polynucleotide sequence described in Table 1. SEQ ID NO:X is identified by an integer specified in column 1 of Table 1. The polypeptide sequence SEQ ID NO:Y is a translated open reading frame (ORF) encoded by polynucleotide SEQ ID NO:X. There are 940 prostate cancer antigen polynucleotide sequences described in Table 1 and shown in the sequence listing (SEQ ID NO:1 through SEQ ID NO:940). Likewise there are 940 polypeptide sequences shown in the sequence listing, one polypeptide sequence for each of the polynucleotide sequences (SEQ ID NO:941 through SEQ ID NO:1880). The polynucleotide sequences are shown in the sequence listing immediately followed by all of the polypeptide sequences. Thus, a polypeptide sequence corresponding to polynucleotide sequence SEQ ID NO:1 is the first polypeptide sequence shown in the sequence listing. The second polypeptide sequence corresponds to the polynucleotide sequence shown as SEQ ID NO:2, and so on. In otherwords, since there are 940 polynucleotide sequences, for any polynucleotide sequence SEQ ID NO:X, a corresponding polypeptide SEQ ID NO:Y can

be determined by the formula X + 940 = Y. In addition, any of the unique "Sequence/Contig ID" defined in column 2 of Table 1, can be linked to the corresponding polypeptide SEQ ID NO:Y by reference to Table 4.

[0027] The polypeptides of the present invention can be composed of amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres, and may contain amino acids other than the 20 gene-encoded amino acids. The polypeptides may be modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous research literature. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of modifications. Polypeptides may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphotidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., Meth Enzymol 182:626-646 (1990); Rattan et al., Ann NY Acad Sci 663:48-62 (1992).)

[0028] The prostate and prostate cancer polypeptides of the invention can be prepared in any suitable manner. Such polypeptides include isolated naturally occurring polypeptides, recombinantly produced polypeptides, synthetically produced polypeptides, or polypeptides produced by a combination of these methods. Means for preparing such polypeptides are well understood in the art.

[0029] The polypeptides may be in the form of the secreted protein, including the mature form, or may be a part of a larger protein, such as a fusion protein (see below). It is often advantageous to include an additional amino acid sequence which contains secretory or leader sequences, pro-sequences, sequences which aid in purification, such as multiple histidine residues, or an additional sequence for stability during recombinant production.

[0030] The prostate and prostate cancer polypeptides of the present invention are preferably provided in an isolated form, and preferably are substantially purified. A recombinantly produced version of a polypeptide, including the secreted polypeptide, can be substantially purified using techniques described herein or otherwise known in the art, such as, for example, by the one-step method described in Smith and Johnson, Gene 67:31-40 (1988). Polypeptides of the invention also can be purified from natural, synthetic or recombinant sources using techniques described herein or otherwise known in the art, such as, for example, antibodies of the invention raised against the polypeptides of the present invention in methods which are well known in the art.

[0031] By a polypeptide demonstrating a "functional activity" is meant, a polypeptide capable of displaying one or more known functional activities associated with a full-length (complete) protein of the invention. Such functional activities include, but are not limited to, biological activity, antigenicity [ability to bind (or compete with a polypeptide for binding) to an anti-polypeptide antibody], immunogenicity (ability to generate antibody which binds to a specific polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide.

[0032] "A polypeptide having functional activity" refers to polypeptides exhibiting activity similar, but not necessarily identical to, an activity of a polypeptide of the present invention, including mature forms, as measured in a particular assay, such as, for example, a biological assay, with or without dose dependency. In the case where dose dependency

does exist, it need not be identical to that of the polypeptide, but rather substantially similar to the dose-dependence in a given activity as compared to the polypeptide of the present invention (i.e., the candidate polypeptide will exhibit greater activity or not more than about 25-fold less and, preferably, not more than about tenfold less activity, and most preferably, not more than about three-fold less activity relative to the polypeptide of the present invention).

[0033] The functional activity of the prostate cancer antigen polypeptides, and fragments, variants derivatives, and analogs thereof, can be assayed by various methods.

[0034] For example, in one embodiment where one is assaying for the ability to bind or compete with full-length polypeptide of the present invention for binding to an antibody to the full length polypeptide antibody, various immunoassays known in the art can be used, including but not limited to, competitive and non-competitive assay systems using techniques such as radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoradiometric assays, gel diffusion precipitation reactions, immunodiffusion assays, in situ immunoassays (using colloidal gold, enzyme or radioisotope labels, for example), western blots, precipitation reactions, agglutination assays (e.g., gel agglutination assays, hemagglutination assays), complement fixation assays, immunofluorescence assays, protein A assays, and immunoelectrophoresis assays, etc. In one embodiment, antibody binding is detected by detecting a label on the primary antibody. In another embodiment, the primary antibody is detected by detecting binding of a secondary antibody or reagent to the primary antibody. In a further embodiment, the secondary antibody is labeled. Many means are known in the art for detecting binding in an immunoassay and are within the scope of the present invention.

[0035] In another embodiment, where a ligand is identified, or the ability of a polypeptide fragment, variant or derivative of the invention to multimerize is being evaluated, binding can be assayed, e.g., by means well-known in the art, such as, for example, reducing and non-reducing gel chromatography, protein affinity chromatography, and affinity blotting. See generally, Phizicky, E., et al., Microbiol. Rev. 59:94-123 (1995). In another embodiment, physiological correlates polypeptide of the present invention binding to its substrates (signal transduction) can be assayed.

[0036] In addition, assays described herein (see Examples) and otherwise known in the art may routinely be applied to measure the ability of polypeptides of the present

invention and fragments, variants derivatives and analogs thereof to elicit polypeptide related biological activity (either in vitro or in vivo). Other methods will be known to the skilled artisan and are within the scope of the invention.

Prostate and Prostate Cancer Associated Polynucleotides and Polypeptides of the Invention

[0037] It has been discovered herein that the polynucleotides described in Table 1 are expressed at significantly enhanced levels in human prostate and/or prostate cancer tissues. Accordingly, such polynucleotides, polypeptides encoded by such polynucleotides, and antibodies specific for such polypeptides find use in the prediction, diagnosis, prevention and treatment of prostate related disorders, including prostate cancer as more fully described below.

[0038] Table 1 summarizes some of the polynucleotides encompassed by the invention (including contig sequences (SEQ ID NO:X) and the related cDNA clones) and further summarizes certain characteristics of these prostate and/or prostate cancer associated polynucleotides and the polypeptides encoded thereby.

TABLE 1

Seq ID No.	Sequence/ Contig ID	Gene Name	Overlap	HGS Nucleotide Start	HGS Nucleotide End	% Id	% Si	Clone ID
1	574130	(AJ223500) nidogen-2 [Homo sapiens] Length = 1375	gnl|PID|e1237850	3	716	87	87	HOECC56
2	637706			3	1025			HJAAT54
3	638162			109	696			HNTMW23
4	684310			10	300			HFXJA96
5	731016	protease [Human endogenous retrovirus K] >sp|P87892|P87892 PROTEASE (FRAGMENT). Length = 334	gnl|PID|e290663	2	370	66	83	HPLBP54
6	827771			188	322			HPFCR50
7	828193	MAGE-3b [Homo sapiens] >gi|533523 MAGE-6 antigen [Homo sapiens] >gnl|PID|d1007417 MAGE-6 protein [Homo sapiens]	gi|499122	237	716	97	97	HMMBI07
8	828194			243	401			HPKAA18
9	828199			2	463			HPJCU04
10	828221	put. LAR preprotein (AA -16 to 1881) [Homo sapiens] >pir|S03841|TDHULK leukocyte antigen-related protein precursor - human Length = 1897	gi|34267	1	1326	100	100	HWHQP39
11	828235			3	248			HWBBB77
12	828236	Gu protein [Homo sapiens] >pir|PC6010|PC6010 RNA helicase Gu - human (fragment) >sp|Q13436|Q13436 NUCLEOLAR RNA HELICASE GU (FRAGMENT). Length = 801	gi|1230564	1	1425	84	84	HWBDP29
13	828237			3	779			HWHPW78

14	828239	(AC002451) pyruvate dehydrogenase kinase isoform 4 [Homo sapiens] >gi|1399197 pyruvate dehydrogenase kinase isoform 4 [Homo sapiens]	gi|2337883	2	433	87	87	HWACS81
15	828242	(AF044321) cytochrome c oxidase assembly protein COX11 [Homo sapiens] >gi|3170264 (AF044321) cytochrome c oxidase assembly protein COX11 [Homo sapiens]	gi|3170264	3	731	100	100	HWBAS37
16	828247	(AF109906) NG22 [Mus musculus] Length = 707	gi|3986770	3	554	39	61	HWBBX45
17	828248	M1 subunit of ribonucleotide reductase [Homo sapiens] >gi|36153 large subunit ribonucleotide reductase [Homo sapiens] >pir|S16680|S16680 ribonucleoside-diphosphate reductase (EC 1.17.4.1) chain M1 - human Length = 792	gi|36065	254	625	82	82	HWBAJ23
18	828250			58	408			HWBBN56
19	828256	put. ribosomal protein L3 (AA 1 - 348) [Homo sapiens] >pir|A27294|R5HUL3 ribosomal protein L3 precursor, mitochondrial - human Length = 348	gi|34754	393	1193	94	94	HUSGZ25
20	828267			3	497			HUSIK57
21	828269			214	492			HUSBF75
22	828272			89	607			HUSYB27
23	828273	(AF047020) alpha-methylacyl-CoA racemase [Homo sapiens] >sp|O43673|O43673 ALPHA-METHYLACYL-COA RACEMASE (EC 5.1.99.4). Length = 380	gi|2896148	300	539	79	89	HULCJ25
24	828290			648	914			HUSGH59
25	828326	Ki antigen [Mus musculus] >gnl|PID|d1029778 (AB007139) PA28 gamma subunit [Mus musculus] >sp|O35563|O35563 KI ANTIGEN. Length = 254	gnl|PID|d1022900	2	970	99	99	HTXJJ72

26	828397			1	942			HLYCG48
27	828405	smooth muscle myosin light chain kinase, smMLCK {C-terminal} [sheep, myometrial tissue, day 127 of gestation, Peptide Partial, 438 aa] [Ovis aries] Length = 438	bbs|175341	37	579	98	100	HLDBK03
28	828461	fra-1 gene product (AA 1-271) [Homo sapiens] >pir|S15750|S15750 transforming protein (fra-1) - human >sp|P15407|FRA1_HUMAN FOS-RELATED ANTIGEN 1. Length = 271	gi|31463	1	873	71	71	HSKEI92
29	828482	Gephyrin [Rattus norvegicus] >pir|JH0681|JH0681 gephyrin - rat >sp|Q03555|GEPH_RAT GEPHYRIN (PUTATIVE GLYCINE RECEPTOR-TUBULIN LINKER PROTEIN). Length = 736	gi|56312	2	940	98	98	HSIGE72
30	828488			64	189			HSDJR78
31	828491			386	586			HSDFC18
32	828492			51	212			HSDGQ64
33	828494			428	733			HSDIC05
34	828496	BS4 peptide [Mus musculus] >sp|P54729|BS4_MOUSE BS4 PROTEIN. Length = 677	gi|863014	3	1097	85	93	HSBAY13
35	828498	14.5 kDa translational inhibitor protein, p14.5 [Homo sapiens] Length = 137	gnl|PID|e1240168	63	500	100	100	HSDXA60
36	828504			173	412			HSAAQ28
37	828507			286	462			HSBCA90
38	828512	CCAAT-box-binding factor [Homo sapiens] >pir|A36368|A36368 transcription factor CBF, CCAAT-binding - human	gi|179969	3	611	82	82	HSAAV04
39	828516	histone H2A [Homo sapiens] >gi|2062704 histone 2A-like protein [Homo sapiens] >gi|2088554 histone 2A-like protein [Homo sapiens]	gnl|PID|e268230	36	458	100	100	HSBAL82

40	828519			142	474			HRGBO34
41	828521	DEAD box-like RNA helicase [Arabidopsis thaliana] >sp|O23251|O23251 DEAD BOX-LIKE RNA HELICASE (FRAGMENT). Length = 450	gnl|PID|e1316345	31	531	38	58	HRGDE67
42	828522	Unknown		361	684			HROBP89
43	828525	cytokine receptor [Homo sapiens] >sp|Q14213|Q14213 CYTOKINE RECEPTOR PRECURSOR.	gi|632974	14	463	99	99	HRGTJ13
44	828529			379	852			HROEB35
45	828530			134	253			HRACZ50
46	828536			84	272			HPYSC02
47	828537			1	270			HPZAA72
48	828539			130	279			HPWDG48
49	828540	ORF_f506 [Escherichia coli] >gi|1789453 (AE000389) aerotaxis sensor receptor, flavoprotein [Escherichia coli]	gi|882594	3	278	100	100	HPWCG66
50	828542			366	626			HRAAA23
51	828543	(AF093263) homer-2a [Homo sapiens] >sp|G3834617|G3834617 HOMER-2A. Length = 343	gi|3834617	3	554	96	97	HPWCS14
52	828544			277	474			HPWDE02
53	828546			1	1302			HPWBZ53
54	828550			61	147			HPWBR44

55	828551			61	585			HPWCG88
56	828553	prostate- specific membrane antigen [Homo sapiens] >pir|A56881|A56881 prostate-specific membrane antigen - human	gi|190664	2	655	95	95	HPWCG57
57	828557	NF-IL6-beta protein [Homo sapiens] >pir|A40225|A40225 transcription activator NF-IL6 beta - human Length = 269	gi|189176	3	359	100	100	HPTVR29
58	828560	T-cell receptor (V-J-C) precursor [Homo sapiens] >pir|A26659|A26659 T-cell receptor gamma-1 chain C region - human {SUB 138-310} >gi|339080 T cell receptor gamma chain [Homo sapiens] {SUB 139-310} >gi|339089 T-cell receptor gamma-chain constant region [Ho	gi|339400	381	683	100	100	HPWAY42
59	828561	zinc finger protein [Homo sapiens] >pir|S47071|S47071 finger protein HZF3, Krueppel-related - human (fragment)	gi|498725	1	204	96	96	HPWBS62
60	828565			3	962			HPWAZ16
61	828566			1214	1423			HPWAJ41
62	828567			204	440			HPRTP24
63	828568	thyroid receptor interactor [Homo sapiens] Length = 286	gi|703112	2	475	97	100	HPRSB55
64	828569	envelope protein [Woodchuck hepatitis B virus] >pir|A03708|SAVLC2 large surface antigen - woodchuck hepatitis virus (clone 2) Length = 431	gi|336133	204	395	38	47	HPWBR81
65	828570			380	580			HPRTH40
66	828571	DY3.6 [Caenorhabditis elegans] >sp|O45323|O45323 DY3.6 PROTEIN. Length = 379	gnl|PID|e1345081	2	670	27	61	HPRTP80
67	828574	rTSbeta [Homo sapiens] >sp|Q15407|Q15407 RTSBETA. Length = 416	gnl|PID|e189422	3	458	89	89	HPRTS71
68	828575			3	209			HPRTI65

69	828577			135	395			HPRTQ68
70	828578	phospholipase A2 [unidentified] >gi|190887 synovial phospholipase A-2 [Homo sapiens] >gi|190889 synovial phospholipase A-2 (EC 3.1.1.4) [Homo sapiens] >pir|A32862|PSHUYF phospholipase A2 (EC 3.1.1.4) precursor, synovial fluid - human >sp|P14555|PA2M_HUMAN	gi|833246	136	627	89	89	HPFCL59
71	828580			2	340			HPRCS86
72	828581			103	339			HPRSB02
73	828583			258	419			HPRTL26
74	828585	HOXB13 [Homo sapiens] Length = 284	gi|1764090	1	285	100	100	HPRCN60
75	828587	(AF043431) retinoblastoma-interacting protein [Homo sapiens] >sp|O75371|O75371 RETINOBLASTOMA-INTERACTING PROTEIN. Length = 897	gi|3452281	139	534	100	100	HPRCF61
76	828590			120	248			HPRCE51
77	828592	breakpoint cluster region protein [Homo sapiens] >sp|Q12844|Q12844 BREAKPOINT CLUSTER REGION PROTEIN (FRAGMENT). Length = 889	gi|487346	48	611	98	98	HPRCF63
78	828593	XP-G factor [Homo sapiens] >pir|S35993|S35993 DNA repair protein XPGC - human >sp|G303059|G303059 XPGC=DNA REPAIR PROTEIN RAD2 HOMOLOG. {SUB 1166-1186} Length = 118	gi|298111	1	1272	87	87	HPRTJ39
79	828594			84	353			HPRCM59
80	828596	homeobox protein [Homo sapiens] >pir|S19010|S19010 homeotic protein PBX3a - human >sp|P40426|PBX3_HUMAN PRE-B-CELL LEUKEMIA TRANSCRIPTION FACTOR-3 (HOMEOBOX PROTEIN PBX3).	gi|35315	1	213	93	93	HPRCH15

		Length = 434						
81	828597	(AL031532) yeast gtr2 homolog, novel small GTPase subfamily protein [Schizosaccharomyces pombe] >sp|O74544|O74544 YEAST GTR2 HOMOLOG, NOVEL SMALL GTPASE SUBFAMILY PROTEIN. Length = 31	gnl|PID|e1319429	1	903	70	85	HPRBB67
82	828598			1	108			HPRAX93
83	828601			2	520			HPRTI75
84	828605			383	601			HPRAY38
85	828608	acid phosphatase [Homo sapiens] Length = 386	gi|189619	21	533	95	96	HPRBF14
86	828609	prostate- specific membrane antigen [Homo sapiens] >pir|A56881|A56881 prostate-specific membrane antigen - human	gi|190664	186	899	100	100	HPRBH58
87	828610	seminal plasma protein precursor [Homo sapiens] >gi|514372 beta-microseminoprotein [Homo sapiens] >gi|825707 prostatic secretory protein (PSP-94) [Homo sapiens]	gi|338415	3	398	100	100	HPRTJ08
88	828617			3	350			HPRAD26
89	828620	prostatic acid phosphatase [Homo sapiens] >gi|189621 acid phosphatase [Homo sapiens] >gi|515997 prostatic acid phosphatase [Homo sapiens]	gi|189613	3	650	94	94	HPRBF16
90	828621			4	126			HPRAG37
91	828622			28	156			HPRAQ51
92	828623			125	313			HPRAG59
93	828625			87	275			HPRAT22
94	828632			68	406			HPQBV63
95	828635			916	1344			HPMGE79

96	828637	(AC005600) PKD1 [Homo sapiens] >sp|O75276|O75276 PKD1 (FRAGMENT). Length = 1339	gi|3522923	1	366	70	71	HPOAB53
97	828639			72	158			HPMDB85
98	828645			2	313			HPJCK50
99	828648	(AF059569) actin binding protein MAYVEN [Homo sapiens] >sp|G3789797|G3789797 ACTIN BINDING PROTEIN MAYVEN. Length = 593	gi|3789797	210	677	32	48	HPJBV55
100	828649	neuropeptide Y [Homo sapiens] >gi|189282 neuropeptide Y [Homo sapiens] >gi|2992498 (AC004485) neuropeptide Y precursor [Homo sapiens]	gi|189274	121	375	100	100	HPWBU56
101	828651	similar to ATPases associated with various cellular activities (AAA);	gnl|PID|e1351769	41	742	51	69	HPJDA05
102	828652			1	189			HPJCY65
103	828655			60	251			HPJBW32
104	828657	(AF061283) neuronal protein 4.1 [Mus musculus] >sp|G3790545|G3790545 NEURONAL PROTEIN 4.1. Length = 879	gi|3790545	38	328	45	67	HPJBD30
105	828660			103	231			HPJCL80
106	828663	calnexin [Homo sapiens] >gi|186523 calnexin [Homo sapiens] >pir|A46673|A46673 calnexin precursor - human >sp|P27824|CALX_HUMAN CALNEXIN PRECURSOR (MAJOR HISTOCOMPATIBILITY COMPLEX CLASS I ANTIGEN-BINDING PROTEIN P88) (P90) (IP90). Length = 592	gi|306481	41	703	87	87	HPJCT42
107	828666			1	246			HPJBI71
108	828668			61	315			HPJBK31
109	828669			1	225			HPJBU60
110	828670			222	350			HPICC36

111	828671	(AJ005866) Sqv-7-like protein [Homo sapiens] >sp|E1360006|E1360006 SQV-7-LIKE PROTEIN (FRAGMENT). Length = 261	gnl|PID|e1360006	3	1025	89	90	HPJAD23
112	828672			1	255			HPICD86
113	828675	MCM4 [Homo sapiens] >sp|G2754697|G2754697 MCM4 (FRAGMENT). Length = 712	gi|2754697	2	2173	99	99	HPJBZ66
114	828677			113	268			HPICC05
115	828678	SNAP43 [Homo sapiens] >gi|1174203 PSE-binding factor PTF gamma subunit [Homo sapiens] >pir|JC6081|JC6081 proximal sequence element-binding transcription factor gamma chain - human >sp|Q16533|Q16533 PSE-BINDING FACTOR PTF GAMMA SUBUNIT. Length = 368	gi|623244	2	664	98	98	HPJAA76
116	828679			142	318			HPJAC93
117	828680	DNA primase (subunit p48) [Homo sapiens] >pir|S45630|S45630 DNA primase chain p48 - human >sp|P49642|PRI1_HUMAN DNA PRIMASE SMALL SUBUNIT (EC 2.7.7.-) (DNA PRIMASE 49 KD SUBUNIT) (P49). >gi|2353692 DNA primase 1 [Homo sapiens] {SUB 97-146} Length = 420	gi|510406	74	652	100	100	HPICG94
118	828681			3	167			HPJAA30
119	828682			3	617			HPIBM51
120	828683			54	329			HPIBR22
121	828686	(AF006010) progestin induced protein [Homo sapiens] >sp|G4101695|G4101695 PROGESTIN INDUCED PROTEIN. Length = 2796	gi|4101695	2	886	95	97	HPIBQ56
122	828687			27	131			HPIBS12

<table>
<tr><td>123</td><td>828688</td><td>CCAAT-box DNA binding protein subunit NF-YB [Homo sapiens] >sp|P25208|CBFA_HUMAN CCAAT-BINDING TRANSCRIPTION FACTOR SUBUNIT A (CBF-A) (NF-Y PROTEIN CHAIN B) (NF-YB) (CAAT-BOX DNA BINDING PROTEIN SUBUNIT B).</td><td>gi|189199</td><td>128</td><td>757</td><td>100</td><td>100</td><td>HPJAA20</td></tr>
<tr><td>124</td><td>828689</td><td>creatine kinase [Homo sapiens] >pir|A31431|A30789 creatine kinase (EC 2.7.3.2) precursor, mitochondrial - human >sp|P12532|KCRU_HUMAN CREATINE KINASE, UBIQUITOUS MITOCHONDRIAL PRECURSOR (EC 2.7.3.2) (U- MTCK) (MIA-CK) (ACIDIC-TYPE MITOCHONDRIAL CREATINE K</td><td>gi|180590</td><td>227</td><td>1222</td><td>84</td><td>84</td><td>HPICC13</td></tr>
<tr><td>125</td><td>828692</td><td>(AJ223301) aralkyl acyl-CoA:amino acid N-acyltransferase [Bos taurus] >gi|2865607 (AF045032) aralkyl acyl-CoA:amino acid N-acyltransferase [Bos taurus] >sp|O46686|O46686 ARALKYL ACYL-COA:AMINO ACID N-ACYLTRANSFERASE (EC 2.3.1.13) (GLYCINE N-ACYLTRANSFERAS</td><td>gnl|PID|e1248977</td><td>278</td><td>1000</td><td>49</td><td>70</td><td>HPIBO30</td></tr>
<tr><td>126</td><td>828693</td><td>dJ14O9.2 (Melanoma-Associated Antigen MAGE LIKE) [Homo sapiens] >sp|O76058|O76058 DJ14O9.2 (MELANOMA-ASSOCIATED ANTIGEN MAGE LIKE). Length = 606</td><td>gnl|PID|e1311294</td><td>1</td><td>426</td><td>45</td><td>69</td><td>HPIBL27</td></tr>
<tr><td>127</td><td>828694</td><td></td><td></td><td>1</td><td>333</td><td></td><td></td><td>HPIBY69</td></tr>
<tr><td>128</td><td>828696</td><td></td><td></td><td>171</td><td>347</td><td></td><td></td><td>HPIBA33</td></tr>
</table>

129	828697	kynurenine/alpha-aminoadipate aminotransferase [Rattus norvegicus] >sp|Q64602|Q64602 KYNURENINE/ALPHA-AMINOADIPATE AMINOTRANSFERASE (EC 2.6.1.7) (KYNURENINE--OXOGLUTARATE AMINOTRANSFERASE) (KYNURENINE AMINOTRANSFERASE). Length = 425	gi|1050752	258	422	61	72	HPICB03
130	828699			3	1109			HPIBL48
131	828702	prostate- specific membrane antigen [Homo sapiens] >pir|A56881|A56881 prostate-specific membrane antigen - human >bbs|164191 prostate-specific membrane antigen,	gi|190664	118	744	76	78	HPIAZ02
132	828703			285	689			HPIBB96
133	828704	put. DNA topoisomerase I (AA 1-864) [Escherichia coli] >gnl|PID|d1015527 DNA topoisomerase I (EC 5.99.1.2) (w-protein) (Relaxing enzyme) (Untwisting enzyme) (Swivelase). [Escherichia coli]	gi|415338	2	406	98	98	HPIBH30
134	828706	mitotic centromere-associated kinesin [Homo sapiens] >sp|Q99661|Q99661 MITOTIC CENTROMERE-ASSOCIATED KINESIN. Length = 725	gi|1695882	559	1788	98	98	HPIBJ11
135	828708			2	589			HPIAW81
136	828711			1	93			HPIAZ32
137	828712			49	309			HPIAU16
138	828713			142	396			HPIAV37
139	828714			68	1849			HPIAV20
140	828715			174	356			HPIAS34
141	828718	ipa-6d gene product [Bacillus subtilis] >gnl|PID|e1186348 alternate gene name: ipa-6d; similar to quinone biosynthesis [Bacillus subtilis]	gi|413930	403	1308	35	57	HPIAL41

142	828723	UDP glucuronosyltransferase precursor [Homo sapiens] >pir|A48633|A48633 dihydrotestosterone/androstanediol UDP-glucuronosyltransferase isoform 3, udpgth-3 - human	gi|475759	3	206	97	100	HPIAL34
143	828726	hydrophobic membrane-bound protein [Escherichia coli] >gi|1147818 part of a molybdenum periplasmic binding protein dependent transport system [Escherichia coli] >gi|973215 ModB [Escherichia coli]	gi|504499	1	255	98	98	HPIAS69
144	828728	(AF044954) NADH:ubiquinone oxidoreductase PDSW subunit [Homo sapiens] >gi|4165091 (AF088991) NADH-ubiquinone oxidoreductase PDSW subunit [Homo sapiens] Length = 172	gi|4164442	1	498	84	86	HPIAS40
145	828730	MAK11 protein [Saccharomyces cerevisiae] >gi|486013 ORF YKL021c [Saccharomyces cerevisiae] >pir|A29938|A29938 MAK11 protein - yeast (Saccharomyces cerevisiae) >sp|P20484|MK11_YEAST MAK11 PROTEIN. Length = 468	gi|171877	394	1569	34	64	HPHAF82
146	828732	rab geranylgeranyl transferase [Homo sapiens] >pir|JC5538|JC5538 Rab geranylgeranyl transferase (EC 2.5.1.-) alpha chain - human >sp|E1256376|E1256376 RAB GERANYLGERANYL TRANSFERASE. Length = 567	gnl|PID|e1256376	155	868	97	97	HPIAN07
147	828733			202	438			HPIAK81
148	828735	(AF006265) cancer associated surface antigen [Homo sapiens] >gnl|PID|d1023440 (AB007619) EBAG9 [Homo sapiens] >sp|O00559|O00559 CANCER ASSOCIATED SURFACE ANTIGEN. Length = 213	gi|2213934	369	1139	90	90	HPIAE30

149	828736			1	132			HPFEA11
150	828739			60	347			HPIAA46
151	828740			2	394			HPIAC69
152	828742			2	475			HPHAB61
153	828748	glandular kallikrein precursor [Homo sapiens] >pir|A29586|A29586 tissue kallikrein (EC 3.4.21.35) hGK-1 precursor - human >sp|P20151|KLK2_HUMAN GLANDULAR KALLIKREIN 2 PRECURSOR (EC 3.4.21.35) (TISSUE KALLIKREIN) (PROSTATE) (HGK-1). Length = 261	gi|386842	3	707	95	96	HPEAB20
154	828749	serine/threonine kinase [Rattus norvegicus] >sp|O08678|O08678 SERINE/THREONINE KINASE. Length = 793	gnl|PID|e290956	443	826	94	99	HPIAA79
155	828752	androgen regulated homeobox protein [Homo sapiens] >sp|Q99801|HK31_HUMAN HOMEOBOX PROTEIN NKX-3.1. Length = 234	gi|1732378	1051	1692	99	99	HPIAA91
156	828753			2	187			HPFEA08
157	828754			423	566			HPFDD83
158	828757			2	409			HPFDI21
159	828761			3	113			HPFDE61
160	828762			3	317			HPFDE33
161	828764	cytochrome c oxidase subunit VIc preprotein [Homo sapiens] >gi|3859868 (AF067637) cytochrome c oxidase subunit VIc [Homo sapiens]	gnl|PID|e223120	51	329	100	100	HPMSH48
162	828765			3	80			HPFDB49
163	828766			90	242			HPFDT61
164	828767			797	937			HPWDK71
165	828768			1109	1324			HPFDD04
166	828770			156	392			HPFDF79

167	828771	(AF001629) WASP interactor protein [Homo sapiens] >sp|G4100621|G4100621 WASP INTERACTOR PROTEIN (FRAGMENT). Length = 328	gi|4100621	1	273	55	61	HPFDS50
168	828772			200	340			HPFDT28
169	828773			115	348			HPFDE85
170	828775			23	208			HPFCR19
171	828776			3	134			HPFCY40
172	828777			131	919			HPFDM39
173	828778			2	121			HPFCZ89
174	828780			46	420			HPFDA70
175	828781			408	734			HPFCP06
176	828782			61	186			HPFDI40
177	828783	relaxin [Homo sapiens] >gi|490063 H1-relaxin [Homo sapiens] >gi|412167 relaxin [Homo sapiens] >gi|512431 preprorelaxin [Homo sapiens] >gi|35933 prepro-relaxin H1 [Homo sapiens]	gi|490056	68	253	70	70	HPFCH80
178	828784			82	321			HPFCT79
179	828785			32	250			HPFCX77
180	828786			302	532			HPFCT31
181	828788			341	538			HPFCI59
182	828790			195	317			HPFCT53
183	828791			6	140			HPFCI14
184	828792			121	801			HPFCC91
185	828794			1219	1440			HPFCJ56
186	828797			128	259			HPFCC42
187	828798			237	350			HPFCI76
188	828799			113	322			HPFAA95
189	828801			90	239			HPEAG41
190	828802			165	392			HPFCL26

191	828803	(AB022017) AMP-activated protein kinase alpha-1 [Homo sapiens] >sp|D1037533|D1037533 AMP-ACTIVATED PROTEIN KINASE ALPHA-1. >gnl|PID|e315274 AMP-activated protein kinase alpha-1 [Homo sapiens] {SUB 294-550}	gnl|PID|d1037533	96	458	83	83	HPFBA83
192	828804			98	286			HPEAC32
193	828805			166	303			HPFCF17
194	828807			1	195			HPFCF96
195	828809			147	236			HPEAC52
196	828810			1	153			HPEBT31
197	828811			283	426			HPFAA06
198	828817			2	160			HPCAC47
199	828818			1	258			HPEAA76
200	828819			345	623			HPEBG44
201	828820			314	502			HPEAB80
202	828821			246	416			HPCAF64
203	828823	spore coat protein SP87 [Dictyostelium discoideum] Length = 677	gi|915203	267	875	44	61	HPEAB79
204	828824			458	643			HPCAC56
205	828825			132	446			HPDDY72
206	828826			2	730			HPCAN60
207	828829			499	672			HPCAO54
208	828830	Arnt [Homo sapiens] >pir|I59550|I59550 Arnt - human >sp|P27540|ARNT_HUMAN ARYL HYDROCARBON RECEPTOR NUCLEAR TRANSLOCATOR (ARNT PROTEIN) (DIOXIN RECEPTOR, NUCLEAR TRANSLOCATOR) (HYPOXIA-INDUCIBLE FACTOR 1 BETA) (HIF-1 BETA). Length = 789	gi|179004	1	219	90	92	HPCAA27
209	828833			42	278			HPCAB16

210	828835			61	474			HOUDC43
211	828838	chordin [Xenopus laevis] >pir|A55195|A55195 chordin precursor - African clawed frog >sp|Q91713|CHRD_XENLA CHORDIN PRECURSOR (ORGANIZER-SPECIFIC SECRETED DORSALIZING FACTOR). Length = 941	gi|603945	2	1468	43	56	HPCAO32
212	828840			536	679			HOVCJ65
213	828845			69	212			HOSDG69
214	828846			3	1034			HSPBQ12
215	828847			36	395			HPEAA46
216	828849	(AF041474) BAF53a [Homo sapiens] >sp|G4001803|G4001803 BAF53A. Length = 429	gi|4001803	62	1468	100	100	HOVCJ86
217	828850	putative [Homo sapiens] >pir|A49364|A49364 59 protein, brain - human (fragment) >sp|Q09019|DMR9_HUMAN DMR-N9 PROTEIN (PROTEIN 59) (FRAGMENT). Length = 553	gi|306712	2	283	97	97	HOUCP33
218	828852			96	437			HOSAZ63
219	828853	(AC004449) R33683_3 [Homo sapiens] >sp|O60372|O60372 R33683_3 (FRAGMENT). Length = 103	gi|2979531	1	465	40	62	HOSAV36
220	828857	uridine kinase [Mus musculus] Length = 260	gi|471981	3	1013	74	88	HOQBM19
221	828861			2	991			HPEAE55
222	828866	enhancer of filmentation 1 [Homo sapiens] >gi|1490787 Crk-associated substrate related protein Cas-L [Homo sapiens] >sp|Q14511|Q14511 ENHANCER OF FILMENTATION 1. Length = 834	gi|1280212	143	637	100	100	HOHBF14

223	828872	pericentriol material 1 [Homo sapiens] >pir|A54103|A54103 centrosome autoantigen PCM-1 - human >sp|Q15154|Q15154 PERICENTRIOL MATERIAL 1. Length = 2024	gi|450277	295	879	93	94	HOHAL47
224	828874	histone H1(0) (aa 1-194) [Homo sapiens] >pir|A24850|HSHU10 histone H1-0 - human >sp|P07305|H10_HUMAN HISTONE H1' (H1.0) (H1(0)). {SUB 2-194} Length = 194	gi|32107	3	902	82	82	HOGBL72
225	828875	myosin VI [Homo sapiens] >sp|G2304981|G2304981 MYOSIN VI. Length = 1262	gi|2304981	1	450	99	99	HOGCC24
226	828877	75 kDa subunit NADH dehydrogenase precursor [Homo sapiens] >pir|S17854|S17854 NADH dehydrogenase (ubiquinone) (EC 1.6.5.3) 75K chain precursor - human	gi|38079	24	275	95	97	HOFMJ67
227	828878	S-adenosylmethionine decarboxylase proenzyme (EC 4.1.1.50) old gene name 'AMD' [Homo sapiens] >pir|A31786|DCHUDM adenosylmethionine decarboxylase (EC 4.1.1.50) precursor - human	gi|178518	282	1325	95	95	HOGCO89
228	828879			2	271			HOEJI17
229	828881			139	969			HOGAF39
230	828885	product possesses binding site dependent transcriptional suppressing activity [Homo sapiens] >pir|A44351|A44351 transcription repressor E4BP4 - human >sp|Q14211|Q14211 E4BP4 GENE. Length = 462	gi|30956	173	1639	94	95	HOEEC58
231	828886			82	228			HODGT65
232	828887	ZNF127-Xp [Homo sapiens] >sp|Q13434|Q13434 ZNF127-XP. Length = 485	gi|1304599	2	1327	56	76	HOECN41

233	828889	neurofibromin [Homo sapiens] >sp|P21359|NF1_HUMAN NEUROFIBROMIN (NEUROFIBROMATOSIS-RELATED PROTEIN NF-1). >gi|736765 neurofibromatosis 1 [Homo sapiens] {SUB 751-1611} >gi|189161 neurofibromatosis protein type 1 [Homo sapiens] {SUB 1168-1566}	gi|292354	265	690	89	89	HODAQ30
234	828891	FAST kinase [Homo sapiens] >pir|I37386|I37386 FAST kinase - human >sp|Q14296|Q14296 FAST KINASE. Length = 549	gi|1006659	84	1238	100	100	HODDG78
235	828899			3	344			HNWAA42
236	828907			3	566			HNTSS75
237	828911			1217	1501			HNTMC68
238	828914	MAP KINASE-ACTIVATED PROTEIN KINASE 2 (EC 2.7.1.-) (MAPK-ACTIVATED PROTEIN KINASE 2) (MAPKAP KINASE 2) (MAPKAPK-2). Length = 400	sp|P49137|MKK2_HUMAN	586	1176	98	99	HNTRL23
239	828917	zinc finger protein 7 (ZFP7) [Homo sapiens] >pir|A34612|A34612 zinc finger protein ZNF7 - human Length = 686	gi|340446	790	1536	57	70	HNTCR38
240	828921	RNA helicase [Homo sapiens] >pir|S71758|S71758 DEAD box protein MrDb, Myc-regulated - human >sp|Q92732|Q92732 RNA HELICASE. Length = 610	gnl|PID|e254454	123	1253	90	90	HNTRO07
241	828922			138	1403			HNTAB76
242	828924	(AE000180) biotin synthesis, sulfur insertion? [Escherichia coli] >gi|490219 BIOB gene product [Escherichia coli] >gnl|PID|e305036 BIOTIN SYNTHASE [Escherichia coli] >pir|JC2517|SYECBB biotin synthetase (EC 2.8.1.-) - Escherichia coli >sp|P12996|BIOB_ECOL	gi|1786992	1	78	95	95	HNHAG14

		>sp|P12996|BIOB_ECOL						
243	828925			376	426			HNGKM39
244	828926			28	522			HNTBH70
245	828928			1	330			HNGNK23
246	828930	casein kinase I-alpha [Homo sapiens] >pir|A57011|A57011 casein kinase I-alpha - human Length = 337	gi|852055	412	1467	89	91	HNFJH94
247	828935	(AL021366) cICK0721Q.3 (Kinesin related protein) [Homo sapiens] >sp|O60887|O60887 CICK0721Q.3 (KINESIN RELATED PROTEIN). >gnl|PID|e1332987 (AJ010479) kinesin-like protein [Homo sapiens] {SUB 1-274} Length = 673	gnl|PID|e1330109	2	1447	86	86	HNTRL26
248	828937	apurinic/apyrimidinic endonuclease [Homo sapiens] >gi|183780 apurinic/apyrimidinic endonuclease [Homo sapiens] >gi|32022 AP endonuclease 1 [Homo sapiens] >bbs|111437 Ref-1=redox factor [human, Peptide, 318 aa] [Homo sapiens] >pir|S23550|S23550 DNA-(apurin	gi|178747	124	1158	95	95	HNTNM15
249	828940	pol polyprotein - Moloney murine leukemia virus (strain 3-1R) (fragment) Length = 559	pir|A46311|A46311	1399	1806	58	71	HNGGG72
250	828942			3	386			HNFHK65

251	828943	rapamycin binding protein [Homo sapiens] >gi|182644 FK506-binding protein 25 [Homo sapiens] >pir|JQ1522|JQ1522 peptidylprolyl isomerase (EC 5.2.1.8) FKBP3 - human >sp|Q00688|FKB3_HUMAN RAPAMYCIN-SELECTIVE 25 KD IMMUNOPHILIN (FKBP25) (PEPTIDYL-PROLYL CIS-T	gi|182626	3	710	100	100	HMWHS08
252	828946	hepatitis delta antigen interacting protein A [Homo sapiens] >sp|Q15834|Q15834 HEPATITIS DELTA ANTIGEN INTERACTING PROTEIN A. Length = 202	gi|1488314	118	729	66	66	HMWHE39
253	828947			199	396			HMWIM20
254	828956	(AF029071) p52 pro-apototic protein [Gallus gallus] Length = 465	gi|2599492	470	1384	74	86	HMWGG82
255	828958			1	306			HMWBS21
256	828965	pterin-4a-carbinolamine dehydratase [Homo sapiens] >gi|848987 pterin-4a-carbinolamine dehydratase [Homo sapiens] >gnl|PID|e1292435 (AJ005542) dimerization cofactor of HNF1; pterin-4a-carbinolamin dehydratase [Rattus norvegicus] >gnl|PID|e1292435 (AJ005542	gi|848985	2	370	100	100	HMWED17
257	828969	Ran-BP1(Ran-binding protein 1) [Homo sapiens] Length = 200	gnl|PID|d1007847	2	742	91	91	HMWFM25
258	828971			574	753			HMVAJ71
259	828973	similar to leucyl-tRNA synthetase;	gnl|PID|e1344085	85	678	74	88	HMUBQ39
260	828980	acidic 82 kDa protein [Homo sapiens] >pir|G01522|G01522 acidic 82 kDa protein - human >sp|Q12987|Q12987 ACIDIC 82 KDA PROTEIN. Length = 736	gi|558458	3	524	88	88	HMTME58

261	828984	high mobility group box [Homo sapiens] >pir|A41976|A41976 structure-specific recognition protein, SSRP1 - human Length = 709	gi|184242	322	2388	97	97	HMUAQ01
262	828985			734	928			HMSGL25
263	828988	Similarity to Yeast MSP1 protein (TAT-binding homolog 4) (SW:MSP1_YEAST) [Caenorhabditis elegans] >sp|P54815|MSP1_CAEEL MSP1 PROTEIN HOMOLOG. Length = 357	gnl|PID|e1347884	1	1137	79	88	HMUBL18
264	828993			78	308			HMTMB67
265	828995			653	1567			HMSIV02
266	829000			296	478			HMMBW26
267	829005			1	531			HMQAI48
268	829009	GTP-binding protein [Homo sapiens] >sp|O43824|O43824 GTP-BINDING PROTEIN. Length = 442	gnl|PID|e1227622	64	927	88	88	HMQAI69
269	829010	(AF035537) DNA polymerase zeta [Homo sapiens] Length = 3052	gi|2665742	282	1262	93	93	HMSGH89
270	829012	ribophorin II precursor - human Length = 631	pir|B26168|B26168	161	2188	94	95	HMSJH16
271	829013			1339	1506			HMIAX25
272	829019			41	223			HMIAJ48
273	829020	similar to WD domain, G-beta repeats (2 domains);	gnl|PID|e1345001	21	800	60	77	HMELR71
274	829021			356	640			HMIAJ26
275	829026	RIZ [Homo sapiens] >sp|Q13029|Q13029 ZINC FINGER PROTEIN RIZ. >pir|I38902|I38902 retinoblastoma-binding protein RIZ - human {SUB 3-1721} Length = 1721	gi|3645905	89	1183	87	87	HMELM45

<table>
<tr><td>276</td><td>829030</td><td>chaperonin-like protein [Homo sapiens] >pir|S48087|S48087 t-complex-type molecular chaperone CCT6 - human >gi|184462 chaperonin-like protein [Homo sapiens] {SUB 143-531} Length = 531</td><td>gi|517065</td><td>1</td><td>1674</td><td>95</td><td>95</td><td>HMICQ08</td></tr>
<tr><td>277</td><td>829035</td><td>(AF082516) I-1 receptor candidate protein [Homo sapiens] >sp|G3462807|G3462807 I-1 RECEPTOR CANDIDATE PROTEIN. >gi|3493225 (AF058290) imidazoline receptor antisera-selected protein [Homo sapiens] {SUB 469-1063} Length = 1504</td><td>gi|3462807</td><td>2</td><td>679</td><td>98</td><td>98</td><td>HMEFK17</td></tr>
<tr><td>278</td><td>829041</td><td>pyrroline-5-carboxylate reductase [Homo sapiens] >pir|A41770|A41770 pyrroline-5-carboxylate reductase (EC 1.5.1.2) - human >sp|P32322|PROC_HUMAN PYRROLINE-5-CARBOXYLATE REDUCTASE (EC 1.5.1.2) (P5CR) (P5C REDUCTASE). Length = 319</td><td>gi|189498</td><td>268</td><td>1032</td><td>99</td><td>100</td><td>HMEIQ04</td></tr>
<tr><td>279</td><td>829045</td><td></td><td></td><td>2</td><td>1771</td><td></td><td></td><td>HMEKR35</td></tr>
<tr><td>280</td><td>829048</td><td></td><td></td><td>115</td><td>1467</td><td></td><td></td><td>HMEJC44</td></tr>
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<tr><td>282</td><td>829052</td><td></td><td></td><td>795</td><td>1154</td><td></td><td></td><td>HMHBD67</td></tr>
<tr><td>283</td><td>829057</td><td></td><td></td><td>116</td><td>799</td><td></td><td></td><td>HMEAF61</td></tr>
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<tr><td>285</td><td>829059</td><td></td><td></td><td>310</td><td>501</td><td></td><td></td><td>HMDAQ69</td></tr>
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<tr><td>287</td><td>829062</td><td>(AF095791) TACC2 protein [Homo sapiens] >sp|G3777596|G3777596 TACC2 PROTEIN (FRAGMENT). Length = 653</td><td>gi|3777596</td><td>1417</td><td>2622</td><td>50</td><td>71</td><td>HMCGK90</td></tr>
<tr><td>288</td><td>829063</td><td>kinesin-like DNA binding protein KID - human Length = 665</td><td>pir|S62328|S62328</td><td>58</td><td>1437</td><td>83</td><td>84</td><td>HMEFH72</td></tr>
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290	829066	37KD protein, similar to YI22-ECOLI [Escherichia coli] >sp|Q47535|Q47535 37KD PROTEIN, SIMILAR TO YI22-ECOLI. Length = 424	gnl|PID|d1013520	600	1427	98	98	HMAHX38
291	829068	(AF037204) RING zinc finger protein [Homo sapiens] >gi|3387925 (AF070558) RING zinc finger protein RZF [Homo sapiens] >sp|O43567|O43567 RING ZINC FINGER PROTEIN. Length = 381	gi|2746333	432	1319	84	84	HMSII92
292	829069			1	207			HLYET39
293	829074			1	1269			HLYDE91
294	829077			181	873			HLYFD84
295	829078	topoisomerase I [Homo sapiens] >gi|473581 DNA topoisomerase I [Homo sapiens] {SUB 5-765} >gnl|PID|e1312191 (AL022394) dJ511B24.1 (Topoisomerase I) [Homo sapiens] {SUB 437-765} Length = 765	gi|339804	2	907	69	78	HLYCP31
296	829079			194	382			HLYBT93
297	829085	putative ATP/GTP-binding protein [Homo sapiens] >sp|Q92989|Q92989 PUTATIVE ATP/GTP-BINDING PROTEIN. Length = 425	gi|1644402	67	783	93	93	HMCEJ41
298	829093	26S proteasome-associated pad1 homolog [Homo sapiens] >sp|O00487|O00487 26S PROTEASOME-ASSOCIATED PAD1 HOMOLOG. Length = 310	gi|1923256	307	1251	100	100	HLYAN96
299	829099	alpha-L-fucosidase precursor (EC 3.2.1.5) [Homo sapiens] >pir|A33427|HWHUFA alpha-L-fucosidase (EC 3.2.1.51) 1 precursor, tissue - human >gnl|PID|e34843 alpha-L-fucosidase [Homo sapiens] {SUB 357-393} Length = 461	gi|178409	2	850	96	96	HLTDK55
300	829101	protein tyrosine phosphatase [Homo sapiens] Length = 415	gi|804750	3	542	100	100	HLYAP23

301	829102	!!!! ALU SUBFAMILY SQ WARNING ENTRY !!!! Length = 593	sp|P39194|ALU7_HUMAN	3	59	84	94	HLTEO83
302	829103			265	663			HLWAC24
303	829104			316	525			HLWAX30
304	829109			3	155			HLTCF21
305	829111			1	333			HLTGS92
306	829115			2	670			HLTHA72
307	829116			104	265			HLQDA07
308	829119			144	374			HLMCG37
309	829120			611	910			HLTGP61
310	829121			558	698			HLQCN32
311	829123	aldehyde oxidase [Homo sapiens] >pir|A49634|A49634 aldehyde oxidase (EC 1.2.3.1) - human >sp|Q06278|ADO_HUMAN ALDEHYDE OXIDASE (EC 1.2.3.1). Length = 1338	gi|438656	7	585	99	99	HLQDA57
312	829126			2	154			HLQCX53
313	829135	beta-D-galactosidase precursor (EC 3.2.1.23) [Homo sapiens] >gi|179423 beta-galactosidase precursor (EC 3.2.1.23) [Homo sapiens] >pir|A32688|A32611 beta-galactosidase (EC 3.2.1.23) precursor - human	gi|179401	3	2090	98	98	HLQAM57
314	829136	(AJ005458) protein Phosphatase 2C beta [Bos taurus] >sp|O62830|O62830 PROTEIN PHOSPHATASE 2C BETA (EC 3.1.3.16). Length = 387	gnl|PID|e1287413	55	1254	95	96	HLTHS28

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<tr><td>315</td><td>829138</td><td>cytochrome b5 [Homo sapiens] >pir|A28936|CBHU5 cytochrome b5, microsomal form - human >sp|P00167|CYB5_HUMAN CYTOCHROME B5. {SUB 2-134} >gi|181229 cytochrome b5 [Homo sapiens] {SUB 87-134} Length = 134</td><td>gi|181227</td><td>35</td><td>499</td><td>89</td><td>89</td><td>HLHTN31</td></tr>
<tr><td>316</td><td>829142</td><td>(AF016509) oxidoreductase [Homo sapiens] >sp|O14756|O14756 OXIDOREDUCTASE. Length = 317</td><td>gi|2338748</td><td>2</td><td>1135</td><td>99</td><td>99</td><td>HLIBJ28</td></tr>
<tr><td>317</td><td>829148</td><td></td><td></td><td>55</td><td>279</td><td></td><td></td><td>HLHDP51</td></tr>
<tr><td>318</td><td>829149</td><td>protein kinase C iota [Homo sapiens] >gi|598225 protein kinase C iota [Homo sapiens] >pir|A49509|A49509 protein kinase C (EC 2.7.1.-) iota - human</td><td>gi|432274</td><td>1</td><td>783</td><td>99</td><td>100</td><td>HLICD11</td></tr>
<tr><td>319</td><td>829156</td><td>ORF YDL063c [Saccharomyces cerevisiae] >pir|S67598|S67598 probable membrane protein YDL063c - yeast (Saccharomyces cerevisiae)</td><td>gnl|PID|e253210</td><td>3</td><td>347</td><td>82</td><td>83</td><td>HLHCD19</td></tr>
<tr><td>320</td><td>829162</td><td>(AF019767) zinc finger protein [Homo sapiens] >sp|O75312|O75312 ZINC FINGER PROTEIN. Length = 459</td><td>gi|3510462</td><td>3</td><td>890</td><td>88</td><td>89</td><td>HLGDA89</td></tr>
<tr><td>321</td><td>829170</td><td></td><td></td><td>2</td><td>160</td><td></td><td></td><td>HLDBY56</td></tr>
<tr><td>322</td><td>829177</td><td>complement factor B [Homo sapiens] >gi|2347133 (AF019413) complement factor B [Homo sapiens] >gi|553536 MHC factor B [Homo sapiens] {SUB 339-509} Length = 764</td><td>gi|291922</td><td>1</td><td>600</td><td>86</td><td>87</td><td>HLDBN31</td></tr>
<tr><td>323</td><td>829179</td><td></td><td></td><td>518</td><td>847</td><td></td><td></td><td>HL2AG36</td></tr>
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324	829184	CDC2 polypeptide (CDC2) (AA 1-297) [Homo sapiens] >gi|29841 CDC2 protein (AA 1-297) [Homo sapiens] >pir|A29539|A29539 protein kinase (EC 2.7.1.37) cdc2 - human >sp|P06493|CC2_HUMAN CELL DIVISION CONTROL PROTEIN 2 HOMOLOG (EC 2.7.1.-) (P34 PROTEIN KINASE)	gi|29839	553	1005	98	98	HL1BD94
325	829185			77	295			HL2AH06
326	829188	M-phase phosphoprotein 4 [Homo sapiens] >sp|Q99545|Q99545 M-PHASE PHOSPHOPROTEIN 4 (FRAGMENT). Length = 611	gnl|PID|e248491	282	1238	92	92	HLAAB63
327	829190	(AF038869) eukaryotic initiation factor 4E-binding protein 3 [Homo sapiens] >sp|O60516|O60516 EUKARYOTIC INITIATION FACTOR 4E-BINDING PROTEIN 3. Length = 100	gi|3169393	3	359	87	87	HL2AG38
328	829193	protein kinase [Homo sapiens] >pir|S34130|S34130 serine/threonine-specific protein kinase PLK (EC 2.7.1.-) - human >sp|P53350|PLK1_HUMAN SERINE/THREONINE-PROTEIN KINASE PLK (EC 2.7.1.-) (PLK-1) (SERINE-THREONINE PROTEIN KINASE 13) (STPK13). Length = 603	gi|312998	2	988	94	94	HL4AF38
329	829196			1	432			HL1AR10
330	829197	TAK1 binding protein [Homo sapiens] >sp|Q15750|Q15750 TAK1 BINDING PROTEIN. Length = 504	gi|1401126	1	252	75	76	HL1BM07

331	829202	(AF060502) peroxisome assembly protein PEX10 [Homo sapiens] >sp|O60683|PEXA_HUMAN PEROXISOME ASSEMBLY PROTEIN PEX10 (PEROXIN-10). Length = 326	gi|3170653	97	465	92	94	HL1AY04
332	829203			1	258			HL1AL88
333	829209			127	342			HL2AF80
334	829210			148	315			HL1AG80
335	829214	cyclin G2 [Homo sapiens] >gi|1236915 cyclin G2 [Homo sapiens] >sp|Q16589|Q16589 CYCLIN G2. Length = 344	gi|1236235	2	484	74	74	HKMSB51
336	829215			29	175			HL1AG81
337	829219			24	290			HL1AG22
338	829220			68	664			HKMMC06
339	829222	(AF016371) U-snRNP-associated cyclophilin [Homo sapiens] >gi|3647230 (AF036331) cyclophilin [Homo sapiens] >sp|O43447|O43447 U-SNRNP-ASSOCIATED CYCLOPHILIN (EC 5.2.1.8). Length = 177	gi|2708309	1	549	100	100	HKGBU67
340	829223			2	187			HL1AC64
341	829225	probable transposase - human transposable element MER37 >pir|S72486|S72486 putative transposase - human transposon MER37 (fragment) {SUB 177-349} Length = 454	pir|S72481|S72481	1607	1720	80	87	HNEBF88
342	829226	pre-B cell enhancing factor [Homo sapiens] >pir|A55927|A55927 pre-B cell enhancing factor - human >sp|P43490|PBEF_HUMAN PRE-B CELL ENHANCING FACTOR PRECURSOR. Length = 491	gi|404013	186	1730	97	97	HKMMZ30
343	829227			285	548			HKIYE27
344	829231			42	92			HKMME67

345	829232	cyclin A [Homo sapiens] >gi|510604 cyclin A [Homo sapiens] >pir|S08277|S08277 cyclin A - human >sp|P20248|CG2A_HUMAN G2/MITOTIC-SPECIFIC CYCLIN A. Length = 432	gi|30307	2	1546	94	95	HKGDC59
346	829233			123	446			HKGBH49
347	829239			141	782			HKFBA66
348	829240			144	347			HKGAB62
349	829242	palmitoyl-protein thioesterase [Homo sapiens] >gi|1314355 palmitoyl protein thioesterase [Homo sapiens] >gi|2465725 (AF022211) palmitoyl-protein thioesterase [Homo sapiens] >sp|P50897|PPT_HUMAN PALMITOYL-PROTEIN THIOESTERASE PRECURSOR (EC 3.1.2.22) (PALMI	gi|1160967	2	955	100	100	HKHAK14
350	829246			68	424			HKAFK34
351	829250			169	309			HKAJW63
352	829253			158	982			HKAHA61
353	829256	(AF094583) putative HIV-1 infection related protein [Homo sapiens] >sp|G3885931|G3885931 PUTATIVE HIV-1 INFECTION RELATED PROTEIN (FRAGMENT). Length = 129	gi|3885931	1043	1831	89	89	HKAFL67
354	829263	histone H4 [Tigriopus californicus] >gi|297562 histone H4 [Chironomus thummi] >gi|7084 histone H4 gene product [Chironomus thummi] >gi|7440 histone H4 [Drosophila hydei] >gnl|PID|e242831 histone H4 [Drosophila hydei] >gnl|PID|e242923 histone H4 [Drosophil	gi|10616	2	361	98	98	HKADJ19

355	829266	similar to S. cerevisiae longevity-assurance protein 1 (SP:P38703) [Caenorhabditis elegans] >sp|Q17870|Q17870 SIMILAR TO S. CEREVISIAE LONGEVITY-ASSURANCE PROTEIN 1. Length = 362	gi|1123105	115	636	43	58	HKADL80
356	829271	cAMP response element regulatory protein [Homo sapiens] >gnl|PID|d1014939 TAXREB67 protein [Homo sapiens] >pir|A45377|A45377 transcription factor CREB-2 - human >sp|P18848|ATF4_HUMAN CYCLIC-AMP-DEPENDENT TRANSCRIPTION FACTOR ATF-4 (DNA-BINDING PROTEIN TAX	gi|181041	261	1118	86	86	HL1AG18
357	829273	unknown [Homo sapiens] >pir|I38891|I38891 hypothetical protein - human (fragment) >sp|Q13021|BENE_HUMAN BENE PROTEIN (FRAGMENT). Length = 148	gi|1000712	1	507	94	94	HKAEP12
358	829274	(AB006202) cytochrome b small subunit of complex II [Homo sapiens] >sp|O14521|DHSD_HUMAN SUCCINATE DEHYDROGENASE [UBIQUINONE] CYTOCHROME B SMALL SUBUNIT PRECURSOR (CYBS) (SUCCINATE-UBIQUINONE REDUCTASE MEMBRANE ANCHOR SUBUNIT). Length = 159	gnl|PID|d1022913	55	546	76	76	HKAPF38
359	829276	Similar to D.melanogaster cadherin-related tumor suppressor [Homo sapiens] >sp|Q92566|Q92566 MYELOBLAST KIAA0279 (FRAGMENT). Length = 2408	gnl|PID|d1014097	272	2422	90	90	HKACB58
360	829279	(AC005620) R33590_2, partial CDS [Homo sapiens] >sp|O75291|O75291 R33590_2, PARTIAL CDS (FRAGMENT). Length = 121	gi|3548790	163	597	95	95	HKAAS81
361	829280			172	375			HJKSB47

362	829283			235	414			HJAAF37
363	829284			2	322			HJMBB19
364	829285			706	912			HKADQ69
365	829287			134	358			HJAAB29
366	829295			81	212			HJACK32
367	829296			352	666			HISAN67
368	829297	mitotic kinase-like protein-1 [Homo sapiens] >pir|S28262|S28262 kinesin-related protein MKLP-1 - human >sp|Q02241|MKLP_HUMAN MITOTIC KINESIN-LIKE PROTEIN-1. Length = 960	gi|34672	1	225	98	98	HJPBA19
369	829298	O-6-methylguanine-DNA methyltransferase [Homo sapiens] >gi|307199 6-O-methylguanine-DNA methyltransferase (EC 2.1.1.63) [Homo sapiens] >gi|34559 O-6-methylguanine-DNA methyltransferase [Homo sapiens] >pir|A34889|XUHUMC methylated-DNA--protein-cysteine S-m	gi|187579	2	694	88	88	HISAV27
370	829302			600	929			HIBEJ72
371	829304			300	716			HKAAL43
372	829320	putative [Homo sapiens] >pir|B41648|B41648 protein-tyrosine-phosphatase (EC 3.1.3.48) cdc25B - human >sp|P30305|MPI2_HUMAN M-PHASE INDUCER PHOSPHATASE 2 (EC 3.1.3.48). >gi|2739200 (AF036233) cdc25B phosphatase [Homo sapiens] {SUB 56-338} Length = 566	gi|180173	161	853	100	100	HIBCJ85

373	829322	capping protein alpha subunit isoform 1 [Homo sapiens] >pir|G02639|G02639 capping protein alpha subunit isoform 1 - human >sp|P52907|CAZ1_HUMAN F-ACTIN CAPPING PROTEIN ALPHA-1 SUBUNIT (CAPZ). Length = 286	gi|1336099	3	938	95	95	HJBCY27
374	829355			3	782			HHEAA46
375	829364	initiation factor 2 alpha [Bos taurus] >gi|204002 translational initiation factor eIF-2, alpha subunit [Rattus norvegicus] >pir|A26711|A26711 translation initiation factor eIF-2 alpha chain - rat >pir|S18461|S18461 translation initiation factor eIF-2 alph	gi|325	70	651	88	88	HKAEV74
376	829919			272	448			HAJAC05
377	829941	weak similarity to procollagen alpha chain 1(V) chain [Caenorhabditis elegans] >sp|Q20220|Q20220 SIMILARITY TO PROCOLLAGEN ALPHA CHAIN 1(V) CHAIN. Length = 697	gi|1065515	215	796	50	74	HAIBC14
378	829945			43	222			HAGHF36
379	829946			2	319			HAHCZ18
380	829947	(AF033188) WSB-2 [Mus musculus] >sp|O54929|O54929 WSB-2. Length = 404	gi|2766493	1	1206	95	98	HAICN24
381	829952			478	741			HAICL28
382	829954	HIV-EP2/Schnurri-2 [Homo sapiens] >gi|187405 MHC binding protein-2 [Homo sapiens] {SUB 1184-1323} Length = 1833	gi|182120	2	853	80	82	HAGDR03
383	829955	zinc finger protein [Homo sapiens] >sp|Q92951|Q92951 ZINC FINGER PROTEIN. Length = 273	gi|1575615	52	885	99	100	HAGEX65
384	829957			1	744			HAGEP17

<table>
<tr><td>385</td><td>829958</td><td>ribosomal protein L22 [Rattus norvegicus] >pir|S52084|S52084 ribosomal protein L22 - rat Length = 128</td><td>gi|710295</td><td>2</td><td>418</td><td>62</td><td>74</td><td>HAECH75</td></tr>
<tr><td>386</td><td>829960</td><td>sorbitol dehydrogenase [Homo sapiens] >gi|1755138 sorbitol dehydrogenase [Homo sapiens] >pir|A54674|A54674 L-iditol 2-dehydrogenase (EC 1.1.1.14) - human >sp|G1755138|G1755138 SORBITOL DEHYDROGENASE. Length = 357</td><td>gi|520450</td><td>2</td><td>1069</td><td>97</td><td>97</td><td>HAIBJ62</td></tr>
<tr><td>387</td><td>829966</td><td>(AF106835) putative DnaJ [Methylovorus sp. strain SS1] >sp|G4008081|G4008081 PUTATIVE DNAJ. Length = 371</td><td>gi|4008081</td><td>185</td><td>505</td><td>40</td><td>74</td><td>HAGAX57</td></tr>
<tr><td>388</td><td>829967</td><td>histone H1 [Homo sapiens] >pir|S26364|HSHU11 histone H1-1 - human >sp|P16403|H1D_HUMAN HISTONE H1D (H1.2). {SUB 2-213} Length = 213</td><td>gi|31968</td><td>213</td><td>542</td><td>81</td><td>81</td><td>HADDI38</td></tr>
<tr><td>389</td><td>829970</td><td></td><td></td><td>3</td><td>878</td><td></td><td></td><td>HADBH65</td></tr>
<tr><td>390</td><td>829981</td><td>transcription factor ATF-3 - human (fragment) Length = 222</td><td>pir|C34223|C34223</td><td>2</td><td>391</td><td>70</td><td>72</td><td>HADFU64</td></tr>
<tr><td>391</td><td>829985</td><td>nuclear RNA helicase [Homo sapiens] >sp|O00148|O00148 NUCLEAR RNA HELICASE. Length = 427</td><td>gi|1905998</td><td>26</td><td>721</td><td>88</td><td>88</td><td>HACBO64</td></tr>
<tr><td>392</td><td>829986</td><td>smooth muscle myosin heavy chain isoform SM1 [human, umbilical cord, fetal aorta, Peptide Partial, 330 aa] [Homo sapiens] >pir|I65768|I65768 smooth muscle myosin heavy chain isoform SM1 - human (fragment) >sp|Q16086|Q16086 SMOOTH MUSCLE MYOSIN HEAVY CHAIN</td><td>bbs|140615</td><td>21</td><td>209</td><td>100</td><td>100</td><td>HACBQ88</td></tr>
<tr><td>393</td><td>829988</td><td></td><td></td><td>325</td><td>849</td><td></td><td></td><td>HACAI04</td></tr>
<tr><td>394</td><td>829990</td><td></td><td></td><td>266</td><td>454</td><td></td><td></td><td>HADFJ12</td></tr>
</table>

395	829991	NGFI-B/nur77 beta-type transcription factor homolog=TINUR [human, T lymphoid cell line, PEER, Peptide, 535 aa] [Homo sapiens] >sp|Q16311|Q16311 TINUR= NGFI-B/NUR77 BETA-TYPE TRANSCRIPTION FACTOR HOMOLOG. Length = 535	bbs|164521	2	286	98	98	HACBV53
396	829992			289	540			HACBX74
397	829993	Not56-like protein [Homo sapiens] >sp|Q92685|NT56_HUMAN NOT56-LIKE PROTEIN. Length = 438	gnl|PID|e276888	3	440	77	77	H6EDW38
398	829998	(AL033385) dna-directed rna polymerase iii subunit [Schizosaccharomyces pombe]	gnl|PID|e1339667	270	830	43	65	H6EDK29
399	829999			14	142			H6BSE17
400	830000	NNP-1 [Homo sapiens] >sp|P56182|NNP1_HUMAN NNP-1 PROTEIN (D21S2056E). Length = 461	gi|2258274	545	856	77	77	H6EEQ39
401	830001	homologous to rat HREV107 (ACC.NO. X76453) [Homo sapiens] Length = 162	gi|1054752	397	903	88	88	H2MBY64
402	830005	alpha 1(XVIII) collagen [Mus musculus] >sp|Q61437|Q61437 PROCOLLAGEN, TYPE XVIII, ALPHA 1 (ALPHA 1 COLLAGEN) (XVIII) (FRAGMENT). Length = 1288	gi|511298	3	347	37	42	H6EEX40
403	830009	TFIIE-beta [Homo sapiens] >bbs|67862 general transcription factor IIE 34 kda subunit, TFIIE 34 kda subunit [human, Peptide, 291 aa] [Homo sapiens] >pir|S29292|S29292 transcription factor TFIIE-beta - human Length = 291	gi|37070	3	1028	93	93	H2LAD85

404	830010	(AF062346) zinc finger protein 216 splice variant 1 [Homo sapiens] >gi|3643811 (AF062347) zinc finger protein 216 splice variant 2 [Homo sapiens] >gi|3668066 (AF062072) zinc finger protein 216 [Homo sapiens] >sp|O76080|O76080 ZINC FINGER PROTEIN 216. >bbs	gi|3643809	1	930	100	100	H2MBU62
405	830127	thymopoietin alpha [Homo sapiens] >pir|A55741|A55741 thymopoietin alpha precursor - human Length = 694	gi|508725	469	1074	77	78	H2MBT25
406	830128			102	770			H2CBH25
407	830129	subunit of coatomer complex [Homo sapiens] >sp|P35606|COPP_HUMAN COATOMER BETA' SUBUNIT (BETA'-COAT PROTEIN) (BETA'-COP) (P102). {SUB 2-906} Length = 906	gi|298097	3	2234	100	100	H2CBU57
408	830137	aldehyde dehydrogenase [Homo sapiens] >sp|P30837|DHA5_HUMAN ALDEHYDE DEHYDROGENASE, MITOCHONDRIAL X PRECURSOR (EC 1.2.1.3) (CLASS 2). Length = 517	gi|1263008	2	943	95	95	H2CBX43
409	830140	retroviral proteinase-like protein - human (fragment) Length = 165	pir|JE0065|JE0065	347	784	100	100	H2CBG30
410	830157	(AF043735) 14-3-3 epsilon [Bos taurus] >gi|984319 epsilon 14-3-3 protein [Homo sapiens] >gnl|PID|d1033501 (AB017103) 14-3-3 epsilon [Homo sapiens] >gi|902787 14-3-3 protein epsilon isoform [Homo sapiens] >gi|1184725 14-3-3 protein epsilon isoform [Homo sa	gi|3676399	2	889	99	99	H2CBB64

411	830195	90kDa heat shock protein [Homo sapiens] >pir|A29461|HHHU84 heat shock protein 90-beta - human >sp|P08238|HS9B_HUMAN HEAT SHOCK PROTEIN HSP 90-BETA (HSP 84) (HSP 90). {SUB 2-724} Length = 724	gi|306891	80	631	93	94	HWACG91
412	830196	90kDa heat shock protein [Homo sapiens] >pir|A29461|HHHU84 heat shock protein 90-beta - human >sp|P08238|HS9B_HUMAN HEAT SHOCK PROTEIN HSP 90-BETA (HSP 84) (HSP 90). {SUB 2-724} Length = 724	gi|306891	19	1263	100	100	H2CAC90
413	830409	eIF3-p40 [Homo sapiens] >gi|2351380 translation initiation factor eIF3 p40 subunit [Homo sapiens] >sp|O15372|O15372 EIF3-P40. Length = 352	gi|2351380	325	1092	91	91	HLDCQ28
414	830417	core protein II precursor [Homo sapiens] >pir|A32629|A32629 ubiquinol--cytochrome-c reductase (EC 1.10.2.2) core protein II - human Length = 453	gi|180928	115	744	81	82	HMCBI54
415	830531	5' half of the product is homologues to Bacillus subtiis SAICAR synthetase, 3' half corresponds to the catalytic subunit of AIR carboxylase [Homo sapiens] >pir|S14147|S14147 multifunctional purine biosynthesis protein - human Length = 425	gi|28384	112	1059	100	100	HMCGQ67
416	830677	pinin [Canis familiaris] >sp|P79149|P79149 PININ. Length = 773	gi|1684845	8	1111	88	88	HLWBS80
417	831355	GTP-binding protein - mouse Length = 198	pir|S39543|S39543	128	730	99	100	HKMAB33
418	831420	(AB016869) p70 ribosomal S6 kinase beta [Homo sapiens] >sp|D1035383|D1035383 P70 RIBOSOMAL S6 KINASE BETA. Length = 495	gnl|PID|d1035383	1	672	91	92	HWBAS06

419	831702	Gem [Homo sapiens] >pir|A54575|A54575 35K GTP-binding protein Gem - human >sp|P55040|GEM_HUMAN GTP-BINDING PROTEIN GEM (GTP-BINDING MITOGEN-INDUCED T-CELL PROTEIN) (RAS-LIKE PROTEIN KIR). Length = 296	gi|544493	100	1107	93	93	H2LAD84
420	831717	ets2 protein [Homo sapiens] >gi|2736087 (AF017257) erythroblastosis virus oncogene homolog 2 protein [Homo sapiens] >pir|B32066|TVHUE2 transcription factor ets-2 - human >sp|P15036|ETS2_HUMAN C-ETS-2 PROTEIN. >gi|182271 ets protein [Homo sapiens] {SUB 324	gi|182273	278	1309	90	90	HLLBB45
421	832488	tissue-specific secretory protein [unidentified] >gi|32051 HE4 protein [Homo sapiens] >pir|S25454|S25454 HE4 protein - human >sp|Q14508|EP4_HUMAN MAJOR EPIDIDYMIS-SPECIFIC PROTEIN E4 PRECURSOR (HE4) (EPIDIDYMAL SECRETORY PROTEIN E4). Length = 125	gi|583141	24	434	98	100	HKMLZ60
422	833207	secretory granule proteoglycan peptide core [Homo sapiens] >gi|338062 proteoglycan secretory granule 1 [Homo sapiens] >gi|32433 hematopoetic proteoglycan core protein (AA 1 - 158) [Homo sapiens] >pir|A35183|A28058 secretory granule proteoglycan core prote	gi|190420	57	542	81	81	HWAFH33
423	835940	putative Rab5-interacting protein {clone L1-57} [human, HeLa cells, Peptide Partial, 122 aa] [Homo sapiens]	bbs|180090	126	464	78	81	HNFHV44
424	836953	GTP-binding protein [Homo sapiens] >pir|G34323|G34323 GTP-binding protein Rab6 - human	gi|550072	388	1038	99	99	HMEFS23

425	837105			860	1168			HL1AS90
426	837300			276	494			HODHJ94
427	837373	ribosomal protein L5 [Homo sapiens] >pir|S55912|S55912 ribosomal protein L5, cytosolic - human >gi|1658578 ribosomal L5 protein [Homo sapiens] {SUB 153-297} Length = 297	gi|550013	1	714	98	98	HIASC92
428	837687	protein trafficking protein [Homo sapiens] >gnl|PID|e239969 transmembrane protein [Homo sapiens] >gnl|PID|e1309760 (AJ004913) integral membrane protein, Tmp21-I (p23) [Homo sapiens] >pir|G01159|G01159 protein trafficking protein tmp21-I - human >sp|E13097	gi|1407826	435	953	98	98	HSLBF05
429	837991			1	294			HPJCY94
430	838442	procollagen C-proteinase [Homo sapiens] >sp|Q13292|Q13292 PROCOLLAGEN C-PROTEINASE. Length = 986	gi|1245357	3	506	97	97	HAUBJ52
431	840541	cyclin C [Homo sapiens] >pir|A40268|A40268 cyclin C - human >sp|P24863|CG1C_HUMAN G1/S-SPECIFIC CYCLIN C. Length = 303	gi|1117984	127	549	99	100	HWHQA57
432	840543	(AF016369) U4/U6 small nuclear ribonucleoprotein hPrp4 [Homo sapiens] >sp|O43445|O43445 U4/U6 SMALL NUCLEAR RIBONUCLEOPROTEIN HPRP4. Length = 522	gi|2708305	40	1020	94	94	HWBEJ29
433	840550			1	141			HWBFM54
434	840563			382	723			HADFY02
435	840565	AZ-1 [Mus musculus] >gnl|PID|d1008454 pre-acrosome localization protein [Mus musculus] >pir|S63993|S63993 acrosomal protein AZ1 - mouse >sp|Q62036|Q62036 5-AZACYTIDINE INDUCED PROTEIN (PRE-ACROSOME LOCALIZATION PROTEIN). Length = 1060	gnl|PID|d1019745	1	300	71	88	HHGCW14

436	840569			2	136			HPRBG41
437	840570	p116Rip [Mus musculus] >sp|P97434|P97434 P116RIP. Length = 1024	gi|1657837	2	691	90	91	HOEDH35
438	840571			873	1097			HIBCA19
439	840573	S-adenosyl homocysteine hydrolase homolog [Homo sapiens] Length = 500	gi|2852125	3	719	74	74	HYAAB09
440	840574			2	292			HWLBN43
441	840575	KERATIN, TYPE I CYTOSKELETAL 10 (CYTOKERATIN 10) (K10) (CK 10). >sp|G244509|G244509 KERATIN 10 V2 SUBDOMAIN 142 AMINO ACID VARIANT. {SUB 452-593} Length = 593	sp|P13645|K1CJ_HUMAN	3	1856	100	100	HWEAD52
442	840579			50	1549			HAPBL12
443	840580			343	867			HWLFE67
444	840581			21	191			HYAAY95
445	840605	(AJ000480) phosphoprotein [Homo sapiens] >sp|O15180|O15180 PHOSPHOPROTEIN (FRAGMENT). Length = 224	gnl|PID|e329709	3	170	97	97	HWTAH85
446	840607	alpha-adaptin (A) (AA 1-977) [Mus musculus] >pir|A30111|A30111 alpha-adaptin A - mouse >sp|P17426|ADAA_MOUSE ALPHA-ADAPTIN A (CLATHRIN ASSEMBLY PROTEIN COMPLEX 2 ALPHA-A LARGE CHAIN) (100 KD COATED VESICLE PROTEIN A) (PLASMA MEMBRANE ADAPTOR HA2/AP2 ADAPT	gi|49878	3	317	98	98	HTYSE72
447	840609	olfactomedin [Rana catesbeiana] >pir|A47442|A47442 olfactomedin precursor - bullfrog >sp|Q07081|OLFM_RANCA OLFACTOMEDIN PRECURSOR (OLFACTORY MUCUS PROTEIN). Length = 464	gi|294502	1	201	46	75	HUFBD83

448	840610	plakoglobin [Homo sapiens] >sp|Q15151|Q15151 PLAKOGLOBIN. >gnl|PID|d1010077 plakoglobin [Homo sapiens] {SUB 239-409} Length = 745	gnl|PID|e214034	1784	2818	94	94	HBGNU40
449	840611			657	848			HUFAT62
450	840612	B-IND1 protein [Mus musculus] >sp|O09003|O09003 B-IND1 PROTEIN. Length = 189	gnl|PID|e1192419	130	1242	85	86	HWLFV07
451	840615	casein kinase II alpha subunit [Bos taurus] >gi|611 casein kinase alpha subunit [Bos taurus] >gi|177994 casein kinase II alpha subunit [Homo sapiens] >gi|598147 casein kinase II alpha subunit [Homo sapiens] >pir|A30319|A30319 casein kinase II (EC 2.7.1.-)	gi|162777	140	1234	94	94	HUKDT16
452	840622			135	962			HTXNQ26
453	840623	1,4-alpha-glucan branching enzyme [Homo sapiens] >pir|A46075|A46075 glycogen branching enzyme - human >sp|Q04446|GLGB_HUMAN 1,4-ALPHA-GLUCAN BRANCHING ENZYME (EC 2.4.1.18) (GLYCOGEN BRANCHING ENZYME) (BRANCHER ENZYME). Length = 702	gi|184026	3	542	97	98	HTTEK41
454	840624			1065	1550			HTXBO36

455	840631	(AL033514) predicted using Genefinder; cDNA EST yk465c10.5 comes from this gene [Caenorhabditis elegans] >sp|E1358418|E1358418 Y75B8A.16 PROTEIN. Length = 431	gnl|PID|e1358418	3	1250	53	73	HTTDU70
456	840632			1241	1453			HTTFY74
457	840633			1	612			HTTFA16
458	840634			232	438			HTTFG83
459	840635			35	748			HTXBW79
460	840636			134	382			HTWBE73
461	840637			315	551			HTTEZ16
462	840639			1035	1700			HTTET75
463	840640	(AC004684) putative ribotol dehydrogenase [Arabidopsis thaliana] >sp|O80924|O80924 PUTATIVE RIBOTOL DEHYDROGENASE. Length = 321	gi|3236237	2	418	31	50	HTQDA44
464	840650			86	940			HTPAG74
465	840652	spermatid perinuclear RNA binding protein [Mus musculus] >pir|A57284|A57284 spermatid perinuclear RNA-binding protein Spnr - mouse >sp|Q62262|Q62262 SPERMATID PERINUCLEAR RNA-BINDING PROTEIN.	gi|673454	1	588	89	89	HTTCB17

		Length = 648						
466	840653			3	989			HTTDG56
467	840655			1	2139			HTPCP50
468	840659	(AF016507) C-terminal binding protein 2 [Homo sapiens] >sp|P56545|CTB2_HUMAN C-TERMINAL BINDING PROTEIN 2. Length = 445	gi|2909777	511	1518	89	89	HTSHI54
469	840660			293	520			HTOJF77
470	840661			3	710			HTLGP71
471	840662	cleavage signal 1 protein [Homo sapiens] >pir|JH0629|JH0629 cleavage signal-1 protein - human >sp|P28290|CS1_HUMAN CLEAVAGE SIGNAL-1 PROTEIN (CS-1). Length = 249	gi|181123	494	1333	90	92	HTOEY44
472	840663			179	466			HTPBY35
473	840670			1132	1647			HTTBJ61
474	840671			210	1001			HTJMJ95
475	840672	(AF037448) Gry-rbp [Homo sapiens] >sp|O60506|O60506 GRY-RBP. Length = 623	gi|3037013	3	1739	99	99	HTHDF09
476	840673	complement component C1s [Homo sapiens] >gi|179648 complement subcomponent C1s precursor [Homo sapiens] >gi|763110 complement protein C1s precursor [Homo sapiens] >pir|A40496|C1HUS complement subcomponent C1s (EC 3.4.21.42) precursor - human >sp|P09871|C1	gi|179646	1	690	98	98	HTJAA66
477	840674	glypican [Homo sapiens] >pir|A36347|A36347 glypican 1 precursor - human >sp|P35052|GLYP_HUMAN GLYPICAN-1 PRECURSOR. Length = 558	gi|31847	208	525	87	87	HTLDZ68

		PRECURSOR. Length = 558						
478	840677			237	1010			HTJNE24
479	840678			3	842			HTGFX11
480	840680	Similarity to H.influenza ribonuclease PH (SW:RNPH_HAEIN);	gnl|PID|e1343517	115	555	48	72	HTLEI30
481	840691	polynucleotide adenylyltransferase [Bos taurus] >sp|P25500|PAP_BOVIN POLY(A) POLYMERASE (EC 2.7.7.19) (PAP) (POLYNUCLEOTIDE ADENYLYLTRANSFERASE). {SUB 2-739} Length = 739	gi|605	1	900	68	70	HTEKG75
482	840700			54	998			HTELT78
483	840701			879	1370			HDQDW52
484	840702			713	955			HTEJY89
485	840705			106	621			HTELU22
486	840715	stanniocalcin [Homo sapiens] >gi|975298 stanniocalcin precursor [Homo sapiens] >sp|P52823|CSTP_HUMAN STANNIOCALCIN PRECURSOR.	gi|1199620	1	828	99	99	HSYBK03
487	840717			561	1058			HSSNA42
488	840718	(AC005154) similar to protein U28928 (PID:g861306) [Homo sapiens] >sp|O75223|O75223 WUGSC:H_DJ0777O23.1 PROTEIN. Length = 188	gi|3242764	227	562	98	98	HSSMV32
489	840719			3	284			HSSNB31
490	840724	metallothionein I-F [Homo sapiens] >gi|386866 human metallothionein-If [Homo sapiens] >pir|B22634|SMHU1F metallothionein 1F - human >sp|P04733|MT1F_HUMAN METALLOTHIONEIN-IF (MT-1F). Length = 61	gi|386867	226	510	100	100	HSVBQ73

METALLOTHIONEIN-IF (MT-1F). Length = 61

491	840725	Unknown		1259	1501			HSRDA46
492	840727			4	606			HSXCO55
493	840731	apg-2 [Mus musculus] >sp|Q61316|HS74_MOUSE HEAT SHOCK 70-RELATED PROTEIN APG-2. Length = 841	gnl|PID|d1013599	22	471	69	75	HSSAO67
494	840733			3	437			HSSGG96
495	840734			228	365			HSRFE65
496	840736	small nuclear ribonucleic protein [Homo sapiens] Length = 92	gi|338259	58	342	100	100	HSRFE95
497	840737			3	341			HSSFS95
498	840739			196	561			HSLJW05
499	840746	similar to mouse CC1. [Homo sapiens] >sp|Q92601|Q92601 MYELOBLAST KIAA0202. Length = 1591	gnl|PID|d1013883	452	1420	85	85	HSLII31
500	840748	cytoplasmic antiproteinase, CAP=38 kda intracellular serine proteinase inhibitor [human, placenta, Peptide, 376 aa] [Homo sapiens] Length = 376	bbs|145232	65	1441	96	96	HSRGX11
501	840750	(AC002339) putative ABC transporter [Arabidopsis thaliana] >sp|O22950|O22950 ABC TRANSPORTER ISOLOG, 3' PARTIAL (FRAGMENT). Length = 664	gi|2335109	507	845	34	62	HSODA53
502	840751	MYOSIN LIGHT CHAIN KINASE, SMOOTH MUSCLE AND NON-MUSCLE ISOZYMES (EC 2.7.1.117) (MLCK) [CONTAINS: TELOKIN]. Length = 1913	sp|Q15746|KMLS_HUMAN	3	2519	90	90	HTEFV12

503	840757	(AB005624) rig-analog DNA-binding protein [Sus scrofa] >gi|306898 rig-analog protein (putative); putative [Homo sapiens] >gi|337416 human homologue of rat insulinoma gene (rig); putative [Homo sapiens]	gnl|PID|d1022359	236	568	100	100	HKBAL84
504	840759	transcription factor ZFM1 [Homo sapiens] >sp|Q15913|Q15913 TRANSCRIPTION FACTOR ZFM1. Length = 571	gi|1100209	481	2073	100	100	HSLDB56
505	840760			233	529			HSKDG51
506	840770	FORMATE ACETYLTRANSFERASE 2 (EC 2.3.1.54) (PYRUVATE FORMATE-LYASE 2) (FRAGMENT). Length = 716	sp|D1036490|D1036490	1	195	100	100	HSLCS52
507	840781	glyoxaslase I [Homo sapiens] >gnl|PID|d1003075 lactoyl glutathione lyase [Homo sapiens] >pir|A46714|A46714 lactoylglutathione lyase (EC 4.4.1.5) - human	gi|183258	107	673	99	99	HSKHK35
508	840789	(AC003003) Homolog of rat B/K protein product [Homo sapiens] >sp|O43330|O43330 HUMAN HOMOLOGUE OF RAT B/K PROTEIN PRODUCT (FRAGMENT). Length = 361	gi|2865208	1	657	93	93	HHPSF20
509	840790			216	347			HJKSC89
510	840791			2	817			HHSGD58
511	840798	polynucleotide phosphorylase (PNPase) [Bacillus subtilis] >gi|1184680 polynucleotide phosphorylase [Bacillus subtilis] >pir|S70691|S70691 polyribonucleotide nucleotidyltransferase (EC 2.7.7.8) alpha chain pnpA - Bacillus subtilis >sp|P50849|PNPA_BACSU POL	gnl|PID|e1185260	2	493	41	66	HHERQ85
512	840802	(AB001915) NG,NG-dimethylarginine dimethylaminohydrolase [Homo sapiens] Length = 285	gnl|PID|d1038106	1	618	97	98	HHFES15

513	840803	zinc finger protein [Molgula oculata] >sp|Q25473|Q25473 ZINC FINGER PROTEIN. Length = 558	gi|308967	1	1935	36	63	HHERC56
514	840809			2	208			HHEPE84
515	840811			1	690			HHFBP51
516	840813			2	214			HHEMJ45
517	840814	(AL022162) dJ454M7.1.1 (Lowe Oculocerebrorenal Syndrome protein OCRL-1) (isoform 1) [Homo sapiens] >gnl|PID|e244699 Lowe oculocerebrorenal syndrome (OCRL) [Homo sapiens] {SUB 336-813} Length = 813	gnl|PID|e1371023	2	154	100	100	HGBIC73
518	840817	(AB004903) STAT induced STAT inhibitor-2 [Homo sapiens] >gi|3265033 (AF037989) STAT-induced STAT inhibitor-2 [Homo sapiens] >sp|O14508|O14508 STAT INDUCED STAT INHIBITOR-2. Length = 198	dbj||AB004903_1	85	864	99	99	HHEBI06
519	840825			2	436			HHEAB14
520	840826			2022	2360			HHBFD61
521	840827			14	817			HHEAH66
522	840828	Cleavage and Polyadenylation Specifity Factor protein [Bos taurus] >sp|P79101|P79101 CLEAVAGE AND POLYADENYLATION SPECIFITY FACTOR PROTEIN. Length = 684	gnl|PID|e225428	2	1180	98	99	HHEAK56
523	840829			130	618			HFVIE96
524	840831			1166	1447			HFXCN75
525	840836			18	566			HFXKK43
526	840837	(AC005757) R32611_2 [Homo sapiens] >sp|O75865|O75865 R32611_2 (FRAGMENT). Length = 160	gi|3688090	322	759	62	80	HGBAG76
527	840838	(AF006386) axonemal dynein light chain [Homo sapiens] >sp|O14645|O14645 AXONEMAL DYNEIN LIGHT CHAIN. Length = 257	gi|2352534	2	832	100	100	HFXJP72

528	840841			2	790			HGAMD29
529	840842			216	791			HFPCK56
530	840843			12	791			HFVGM54
531	840845			669	1031			HGBBY80
532	840847			151	1044			HFPCN94
533	840851			470	2047			HFOXS46
534	840853			15	224			HFOXV75
535	840854			149	1183			HFPBK03
536	840858	(AC002333) molybdenum cofactor biosynthesis protein E isolog [Arabidopsis thaliana] >sp|O22827|O22827 MOLYBDENUM COFACTOR BIOSYNTHESIS PROTEIN E ISOLOG. Length = 198	gi|2281094	249	833	41	51	HFPCP42
537	840859	Gu protein [Homo sapiens] >pir|PC6010|PC6010 RNA helicase Gu - human (fragment) >sp|Q13436|Q13436 NUCLEOLAR RNA HELICASE GU (FRAGMENT). Length = 801	gi|1230564	3	1163	63	74	HFOYQ50
538	840863			1	165			HFIIW33
539	840868	argininosuccinate lyase [Homo sapiens] >gi|179091 argininosuccinate lyase [Homo sapiens] >pir|A31658|WZHURS argininosuccinate lyase (EC 4.3.2.1) - human Length = 464	gi|179089	2	1678	99	99	HFKEN53
540	840869	(AF064244) intersectin long form [Homo sapiens] >sp|G3859855|G3859855 INTERSECTIN LONG FORM. >gi|3859853 (AF064243) intersectin short form [Homo sapiens] {SUB 1-1220} >gi|3930533 (AF064247) intersectin long form [Homo sapiens] {SUB 1209-1263} Length = 172	gi|3859855	33	632	74	88	HFKFG36
541	840870			505	831			HFKFN13
542	840875			3	617			HFITH86

543	840876	(AC004392) Contains similarity to gb|U51898 Ca2+-independent phospholipase A2 from Rattus norvegicus. [Arabidopsis thaliana] >sp|O80693|O80693 F8K4.6 PROTEIN. Length = 1265	gi|3367519	1	1110	45	70	HFIZQ25
544	840881	histone H2B.1 [Homo sapiens] >gnl|PID|e1301465 (AJ223353) Histone H2B [Homo sapiens] >gi|51306 histone H2B-291B (AA 1 - 126) [Mus musculus] >pir|S04153|S04153 histone H2B (clone 291B) - mouse >pir|F40335|F40335 histone H2B.1 (b) - human >sp|E1301465|E1301	gi|184080	3	449	77	77	HFIIR54
545	840883			3	428			HFIHA80
546	840886	(AJ000506) Homeodomain protein Meis2c [Mus musculus] >sp|P97367|MEI2_MOUSE HOMEOBOX PROTEIN MEIS2 (MEIS1-RELATED PROTEIN 1). Length = 477	gnl|PID|e330082	71	964	90	90	HHPDW66
547	840887			1202	1600			HFIIR82
548	840891	RNA polymerase I subunit A12.2 [Saccharomyces cerevisiae] >gi|1019685 ORF YJR063w [Saccharomyces cerevisiae] >gi|531231 RNA polymerase I A12.2 subunit [Saccharomyces cerevisiae] >gi|1015737 ORF YJR063w [Saccharomyces cerevisiae] >pir|A48107|A48107 DNA-dir	gi|172462	250	375	64	86	HFCBQ77
549	840892	histone H2B [Homo sapiens] >pir|I37445|I37445 histone H2B.1 - human >sp|P33778|H2B0_HUMAN HISTONE H2B.1. {SUB 2-126} Length = 126	gi|31977	3	410	98	98	HFEBK16

550	840894	(AF002697) E1B 19K/Bcl-2-binding protein Nip3 [Homo sapiens] >sp|O14620|O14620 E1B 19K/BCL-2-BINDING PROTEIN NIP3. Length = 194	gi|2511529	1	705	80	80	HFIHO60
551	840896	Cdc73p [Saccharomyces cerevisiae] >pir|S59383|S59383 probable membrane protein YLR418c - yeast (Saccharomyces cerevisiae) >sp|Q06697|Q06697 CHROMOSOME XII COSMID 9931. Length = 393	gi|632679	425	1249	28	57	HFIAL02
552	840897	syntaxin-4 [Homo sapiens] >gnl|PID|e332032 (AJ000541) syntaxin 4 precursor [Homo sapiens] >gi|2570870 (AF026007) syntaxin 4 [Homo sapiens] >pir|S52726|S52726 syntaxin-4 - human Length = 297	gi|758105	3	1142	100	100	HFIAW49
553	840898			2	265			HFEBI76
554	840904			396	1802			HETIW62
555	840905	DNA fragmentation factor-45 [Homo sapiens] >sp|O00273|DF45_HUMAN DNA FRAGMENTATION FACTOR-45 (DFF-45). Length = 331	gi|2065561	3	1100	95	95	HETBS69
556	840908	KIAA0156 gene product is related to Xenopus nucleolin. [Homo sapiens] >sp|Q15020|Q15020 ORF. Length = 963	gnl|PID|d1010577	348	2081	87	87	HETCI63
557	840909	3-methyl-adenine DNA glycosylase [Homo sapiens] Length = 298	gnl|PID|e224269	2	949	94	94	HEQAN83
558	840910			103	348			HFKHD68
559	840912			1530	1754			HHPBB92
560	840916	MAL protein [Homo sapiens] >gi|435478 MAL-a gene product [Homo sapiens] >gnl|PID|e1192240 MAL [Homo sapiens] >pir|A29472|A29472 T-cell surface glycoprotein MAL, splice form a - human	gi|307157	1	432	86	93	HETJW92

561	840917			518	886			HETIZ12
562	840918	(AF020038) NADP-dependent isocitrate dehydrogenase [Homo sapiens] >gi|3641398 (AF020038) NADP-dependent isocitrate dehydrogenase [Homo sapien	gi|3641398	231	1508	99	99	HAJCO38
563	840922			839	1033			HELGB82
564	840923			1044	1289			HEQAN39
565	840927			119	364			HEMFU44
566	840928			2	1258			HEMCG01
567	840929	helix-loop-helix phosphoprotein [Homo sapiens] >gi|292055 helix-loop-helix phosphoprotein [Homo sapiens] >pir|I53020|I53020 G-0/G-1 switch regulatory protein 8 - human >pir|I65984|I65984 helix-loop-helix phosphoprotein - human Length = 211	gi|292037	3	662	92	92	HEOMQ95
568	840930	(AF002282) alpha-actinin-2 associated LIM protein [Homo sapiens] >sp|O60440|O60440 ALPHA-ACTININ-2 ASSOCIATED LIM PROTEIN. Length = 316	gi|3138924	3	1019	99	99	HEGAD28
569	840931	similar to thiolesterase;	gnl|PID|e1343797	1	1164	49	67	HEMFC70
570	840941			2	781			HEGAL15
571	840944	cofactor E [Homo sapiens] >sp|Q15813|Q15813 COFACTOR E. Length = 527	gi|1465772	822	1685	98	98	HELFC44
572	840945			1067	1435			HEEAS77
573	840948	lanosterol synthase [human, fetal liver, Peptide, 732 aa] [Homo sapiens] >gnl|PID|d1010523 lanosterol synthase [Homo sapiens] >gi|951314 2,3-oxidosqualene-lanosterol cyclase [Homo sapiens] >pir|JC4194|JC4194 lanosterol synthase (EC 5.4.99.7) - human >sp|P	bbs|176180	3	326	99	100	HE9ST22

574	840949	(AJ005324) glutamate permease [synthetic construct] >gnl|PID|e1360147 (AJ005327) glutamate permease [synthetic construct] >gnl|PID|e1360153 (AJ005330) glutamate permease [synthetic construct] Length = 459	gnl|PID|e1360141	3	101	95	95	HE9RM92
575	840953	P43=mitochondrial elongation factor homolog [human, liver, Peptide, 452 aa] [Homo sapiens] >pir|I53499|I53499 translation elongation factor TU-like protein P43, mitochondrial - human Length = 452	bbs|160014	1	1437	100	100	HELGM94
576	840954	RNase L inhibitor (clone 8) - human Length = 599	pir|S63672|S63672	69	1949	95	95	HE9HC20
577	840958	FUSE binding protein 2 [Homo sapiens] >sp|Q92945|Q92945 FUSE BINDING PROTEIN 2 (FRAGMENT). Length = 652	gi|1575607	154	465	57	58	HFLVB33
578	840960	phosphomannose isomerase [Homo sapiens] >pir|S41122|S41122 mannose-6-phosphate isomerase (EC 5.3.1.8) - human >sp|P34949|MANA_HUMAN MANNOSE-6-PHOSPHATE ISOMERASE (EC 5.3.1.8) (PHOSPHOMANNOSE ISOMERASE) (PMI) (PHOSPHOHEXOMUTASE). {SUB 2-423} Length = 423	gi|416017	224	670	100	100	HEEAD70
579	840968			375	2222			HEBFH29
580	840969			1054	1530			HE9PB53
581	840972			1	387			HE8UU14
582	840973			548	874			HE9DH68
583	840975			1	159			HE9GO90
584	840978			1433	1765			HE9NG78

585	840980	nerve growth factor [Homo sapiens] >gi|32031 pleiotrophin [Homo sapiens] >bbs|119887 pleiotrophin, PTN [human, Peptide, 168 aa] [Homo sapiens] >bbs|130735 heparin-binding neurite outgrowth promoting factor, HBNF {alternatively spliced} [human, Peptide, 16	gi|183890	75	833	90	90	HEBFE14
586	840982			81	359			HE8ES49
587	840985			3	830			HE8UK50
588	840989	(AB016247) sterol-C5-desaturase [Homo sapiens] >sp|O75845|O75845 STEROL-C5-DESATURASE (EC 1.3.3.2) (LATHOSTEROL OXIDASE). Length = 299	gnl|PID|d1034698	107	1027	99	100	HE8FM74
589	840991	(AF032886) forkhead protein [Homo sapiens] >sp|O43524|O43524 FORKHEAD PROTEIN. Length = 673	gi|2895494	861	1559	81	81	HE8FA09
590	840996	ATP:citrate lyase [Homo sapiens] >sp|Q13037|Q13037 ATP:CITRATE LYASE. Length = 1101	gi|603074	818	1906	99	99	HE8MY23
591	840997	LIV-1 protein [Homo sapiens] >pir|G02273|G02273 LIV-1 protein - human >sp|Q13433|Q13433 ESTROGEN REGULATED LIV-1 PROTEIN. Length = 752	gi|1256001	3	1193	75	75	HE8DR57
592	840998			1	390			HE2BN26
593	840999			855	1013			HE8DJ30
594	841000			1	279			HE6DC57
595	841002			363	812			HE8BT63
596	841003			94	315			HE2DX28
597	841008	Aop1_Human, MER5(Aop1_Mouse)-like protein [Homo sapiens] >gi|854126 humer [Homo sapiens] {SUB 227-256} Length = 256	gnl|PID|d1008985	1	672	99	99	HE8AU49

598	841013	(AB011004) UDP-N-acetylglucosamine pyrophosphorylase [Homo sapiens] >sp|Q16222|Q16222 AGX-1 ANTIGEN (FRAGMENT). Length = 505	gnl|PID|d1032151	265	1836	99	99	HDTAU64
599	841014	fumarase precursor [Homo sapiens] >gi|4097195 fumarase [Homo sapiens] >sp|P07954|FUMH_HUMAN FUMARATE HYDRATASE, MITOCHONDRIAL PRECURSOR (EC 4.2.1.2) (FUMARASE). >sp|G4097195|G4097195 FUMARASE (EC 4.2.1.2). Length = 510	gi|1545996	178	1185	96	96	HE2EB32
600	841015			48	425			HE2DT31
601	841018			1	150			HE2EA79
602	841019			94	228			HDTGC76
603	841024	Ran [Canis familiaris] >gi|190879 ras-like protein [Homo sapiens] >gi|2967848 (AF052578) androgen receptor associated protein 24 [Homo sapiens] >gi|727167 Ran [Mus musculus] >bbs|180269 GTP-binding protein [mice, C3H/HeJ spleens, LDS responder, Peptide, 2	gi|924	34	750	100	100	HE9CO25
604	841025			75	401			HDTDZ04
605	841026			3	599			HDTGP42
606	841027			1	489			HDRMB48
607	841029	Id-2H [Homo sapiens] >pir|A40227|A40227 transcription repressor Id-2 - human >sp|Q02363|ID2_HUMAN DNA-BINDING PROTEIN INHIBITOR ID-2. Length = 134	gnl|PID|d1003496	1	528	100	100	HDTAG94
608	841030			515	721			HDTGK45
609	841031			23	145			HDSAL27

610	841034	G-rich sequence factor-1 [Homo sapiens] >gi|517196 G-rich sequence factor-1 [Homo sapiens] >sp|Q12849|GRF1_HUMAN G-RICH SEQUENCE FACTOR-1 (GRSF-1). >pir|S48081|S48081 GRSF-1 protein - human (fragment) {SUB 94-424} Length = 424	gi|517196	267	449	95	98	HDQDH60
611	841036			1201	1542			HDPTM31
612	841039	(AC002340) putative RNA helicase A, 5' partial [Arabidopsis thaliana] >sp|O49345|O49345 PUTATIVE RNA HELICASE A, 5' PARTIAL (FRAGMENT). Length = 1114	gi|2880057	763	2112	60	76	HDQFB71
613	841040	(AF071202) ABC transporter MOAT-B [Homo sapiens] >sp|G3335173|G3335173 ABC TRANSPORTER MOAT-B. Length = 1325	gi|3335173	2	1339	92	92	HDQDF77
614	841048			1	1338			HDPXU60
615	841049	(AC003682) ZNF134 [Homo sapiens] >sp|G2689444|G2689444 ZNF134. Length = 427	gi|2689444	3	347	97	97	HDPXK77
616	841050			705	947			HDPUP64
617	841052	monoamine oxidase A [Homo sapiens] >gi|187353 monoamine oxidase A [Homo sapiens] >gi|187355 monoamine oxidase A [Homo sapiens] >pir|A36175|A36175 amine oxidase (flavin-containing) (EC 1.4.3.4) A - human >sp|P21397|AOFA_HUMAN AMINE OXIDASE [FLAVIN-CONTAINI	gi|187351	1	1194	95	95	HDPRJ46
618	841054			60	1262			HDPXL80
619	841055			23	346			HDPMK92
620	841056			492	695			HDPVB33
621	841060			612	851			HDPXB24

<table>
<tr><td>622</td><td>841061</td><td>quinone oxidoreductase [Homo sapiens] >gi|516534 quinone oxidoreductase2 [Homo sapiens] >pir|A32667|A32667 NAD(P)H dehydrogenase (quinone) (EC 1.6.99.2) 2 - human Length = 231</td><td>gi|190818</td><td>21</td><td>614</td><td>100</td><td>100</td><td>HPIBQ60</td></tr>
<tr><td>623</td><td>841062</td><td>histone deacetylase HD1 [Homo sapiens] >sp|Q13547|HDA1_HUMAN HISTONE DEACETYLASE 1 (HD1). Length = 482</td><td>gi|1277084</td><td>67</td><td>1530</td><td>90</td><td>90</td><td>HDPPA96</td></tr>
<tr><td>624</td><td>841063</td><td>(AL009194) SWISS-PROT:P38861; NONSENSE-MEDIATED MRNA DECAY PROTEIN 3.; SACCHAROMYCES CEREVISIAE</td><td>gnl|PID|e1251068</td><td>2</td><td>592</td><td>69</td><td>82</td><td>HDPJQ57</td></tr>
<tr><td>625</td><td>841067</td><td>mannosyl-oligosaccharide 1,2-alpha-mannosidase (EC 3.2.1.113) - rabbit (fragment) >gi|474282 mannosyl-oligosaccharide alpha-1,2-mannosidase [Oryctolagus cuniculus] {SUB 12-480} Length = 480</td><td>pir|B54408|B54408</td><td>2</td><td>592</td><td>59</td><td>83</td><td>HDPQE64</td></tr>
<tr><td>626</td><td>841074</td><td>14.3.3 protein [Homo sapiens] >gi|32464 HS1 gene product [Homo sapiens] >pir|S15076|S15076 protein kinase regulator 14.3.3 - human >sp|P27348|143T_HUMAN 14-3-3 PROTEIN TAU (14-3-3 PROTEIN THETA) (14-3-3 PROTEIN T-CELL) (HS1 PROTEIN). >gi|3387922 (AF070556</td><td>gi|23222</td><td>188</td><td>907</td><td>98</td><td>99</td><td>HE8NS76</td></tr>
<tr><td>627</td><td>841076</td><td></td><td></td><td>96</td><td>755</td><td></td><td></td><td>HDPMG95</td></tr>
<tr><td>628</td><td>841081</td><td>(AE000715) ribosomal protein L20 [Aquifex aeolicus] >pir|C70382|C70382 ribosomal protein L20 - Aquifex aeolicus >sp|O67086|O67086 50S RIBOSOMAL PROTEIN L20. Length = 118</td><td>gi|2983472</td><td>2</td><td>541</td><td>41</td><td>65</td><td>HDPQC09</td></tr>
<tr><td>629</td><td>841083</td><td></td><td></td><td>1</td><td>480</td><td></td><td></td><td>HDPCX80</td></tr>
<tr><td>630</td><td>841089</td><td></td><td></td><td>321</td><td>551</td><td></td><td></td><td>HDPND16</td></tr>
</table>

631	841093	(AF035646) Rab10 [Mus musculus] >sp|O88386|O88386 RAB10. Length = 200	gi|3406428	479	1132	100	100	HDPPI29
632	841097	(AF090867) guanosine monophosphate reductase [Rattus norvegicus] >sp|G3907579|G3907579 GUANOSINE MONOPHOSPHATE REDUCTASE. Length = 345	gi|3907579	267	1061	78	90	HDPFB78
633	841098	GATA-binding protein [Homo sapiens] >pir|A40815|A40815 transcription factor GATA-2 (version 1) - human >sp|P23769|GAT2_HUMAN ENDOTHELIAL TRANSCRIPTION FACTOR GATA-2. Length = 480	gi|182996	1	384	90	91	HDABX64
634	841101	phosphatidylcholine transfer protein [Bos taurus] >pir|A91092|EPBO phosphatidylcholine transfer protein - bovine >sp|P02720|PPCT_BOVIN PHOSPHATIDYLCHOLINE TRANSFER PROTEIN (PC-TP). Length = 213	gi|710419	3	1004	35	55	HDPBQ32
635	841113	2-hydroxyhepta-2,4-diene-1,7-dioate isomerase (hpcE) [Methanococcus jannaschii] >pir|F64506|F64506 2-hydroxyhepta-2,4-diene-1,7-dioate isomerase homolog - Methanococcus jannaschii >sp|Q59050|Q59050 HYPOTHETICAL PROTEIN MJ1656. Length = 237	gi|1500558	133	1137	50	74	HDBAE85
636	841115			58	396			HDLAZ62
637	841116			47	682			HDPBJ61
638	841117			1	1179			HDFMB93
639	841125			1	117			HCYBI78
640	841127			2	859			HDABQ85

641	841128	collagenase stimulatory factor [Homo sapiens] >gi|1209374 amino acid feature: intracellular domain, aa 707 .. 829; amino acid feature: transmembrane domain, aa 638 .. 706; amino acid feature: extracellular domain, aa 86 .. 637 [Homo sapiens] >gi|34449 M6	gi|409357	64	891	100	100	HDPFH18
642	841132			1	1428			HDPFI70
643	841133	myosin-I, Myr 1c (alternatively spliced) - rat Length = 1078	pir|B45439|B45439	4	1710	89	91	HCYBL17
644	841134	gamma SNAP [Homo sapiens] Length = 312	gi|1685288	2	802	100	100	HDAAC32
645	841135	homologous to mouse gene PC326:GenBank Accession Number M95564 [Homo sapiens] >sp|Q12839|Q12839 (H326). Length = 597	gi|458692	124	765	81	81	HDABE30
646	841136			514	735			HCQDF95
647	841138	imogen 38 [Homo sapiens] >sp|Q92665|Q92665 IMOGEN 38. Length = 395	gnl|PID|e218584	3	1238	80	80	HDABK25
648	841139			347	478			HCQBH60
649	841141			192	833			HDPBQ85
650	841142			452	1051			HCQAM05
651	841145			1022	1366			HCNSQ35
652	841146			864	1061			HCMSW06
653	841150	(AF038957) translation initiation factor 4e [Homo sapiens] >sp|O75349|O75349 TRANSLATION INITIATION FACTOR 4E. Length = 236	gi|3329384	115	387	83	86	HCQAG10

654	841153	argininosuccinate synthetase [Homo sapiens] >gi|28872 argininosuccinate synthetase (aa 1-412) [Homo sapiens] >pir|A01195|AJHURS argininosuccinate synthase (EC 6.3.4.5) - human >sp|P00966|ASSY_HUMAN ARGININOSUCCINATE SYNTHASE (EC 6.3.4.5) (CITRULLINE--ASPA	gi|179057	1207	2532	96	96	HCYBC10
655	841154	(AF084260) signalosome subunit 2 [Homo sapiens] >gi|3639069 (AF087688) alien-like protein [Mus musculus] >sp|O88950|O88950 ALIEN-LIKE PROTEIN. >sp|G3514097|G3514097 SIGNALOSOME SUBUNIT 2. >gi|3309166 (AF071312) COP9 complex subunit 2 [Mus musculus] {SUB 4	gi|3514097	1	1368	100	100	HCMSB29
656	841156	carcinoma-associated antigen GA733-2 [Homo sapiens] >gi|182906 carcinoma-associated antigen GA733-2 [Homo sapiens] >pir|B48149|B48149 epithelial glycoprotein antigen GA733-2 precursor - human Length = 314	gi|182896	6	1130	86	86	HCIAA60
657	841157	collagen pro-alpha-1 type I chain [Mus musculus] >pir|S57243|S21626 collagen alpha 1(I) chain precursor - mouse >sp|P11087|CA11_MOUSE PROCOLLAGEN ALPHA 1(I) CHAIN PRECURSOR. >gi|192262 pro-alpha-1 type I collagen [Mus musculus] {SUB 518-1128} >gi|192264 p	gi|470674	88	336	36	42	HCHCJ07
658	841159			510	818			HCLCK84
659	841164			2	463			HCHAZ66
660	841167			982	1305			HCHOG20

661	841170	SRp30c [Homo sapiens] >gnl|PID|e1248292 (AL021546) pre-mRNA splicing factor SRp30c [Homo sapiens] >gi|4099429 splicing factor SRp30c [Homo sapiens] >pir|S59075|S59075 splicing factor SRp30c - human >sp|G4099429|G4099429 SPLICING FACTOR SRP30C. Length = 22	gi|1049078	2	760	81	81	HCHOE21
662	841173	spermidine synthase [Homo sapiens] >pir|A32610|A32610 spermidine synthase (EC 2.5.1.16) - human Length = 302	gi|338394	2	931	97	97	HCHBQ07
663	841176			561	683			HCFOI36
664	841178	thyroid receptor interactor [Homo sapiens] Length = 152	gi|703110	65	460	99	100	HCGBQ34
665	841180	(AF029777) hGCN5 [Homo sapiens] >sp|G3220164|G3220164 HGCN5. >gi|1491935 histone acetyltransferase [Homo sapiens] {SUB 362-837} >sp|G1911495|G1911495 HGCN5=TRANSCRIPTIONAL ADAPTOR. {SUB 411-837} Length = 837	gi|3220164	553	1530	97	97	HCGLC82
666	841181			2	283			HCFMN22
667	841182	70 K protein (AA 1-614) [Homo sapiens] >pir|A25707|A25707 U1 snRNP 70K protein - human >gi|337447 small ribonucleoprotein 70 kd protein [Homo sapiens] {SUB 178-614} >gi|602021 hU1-70K protein (302 AA) [Homo sapiens] {SUB 227-527} Length = 614	gi|36100	251	988	100	100	HCFNJ56
668	841185			342	536			HCFNF67
669	841187			458	1096			HCGAA74
670	841188	DNA repair endonuclease subunit [Homo sapiens] Length = 905	gi|1524411	2	2749	92	92	HCFMK76
671	841189			336	926			HCFMC34

672	841192	methylmalonyl-CoA mutase [Homo sapiens] >sp|P22033|MUTA_HUMAN METHYLMALONYL-COA MUTASE PRECURSOR (EC 5.4.99.2) (MCM). Length = 750	gi|187452	1	1428	99	99	HCFMO54
673	841194	(AF039405) arsenite-translocating ATPase [Mus musculus] >sp|O54984|O54984 ARSENITE-TRANSLOCATING ATPASE. Length = 350	gi|2745900	182	1138	95	95	HCGAB52
674	841195			3	623			HCEWM29
675	841198			2	913			HCFBC32
676	841200	(AF015037) endooligopeptidase A related protein; EOPA related protein [Oryctolagus cuniculus] >sp|O46480|O46480 ENDOOLIGOPEPTIDASE A RELATED PROTEIN (FRAGMENT). Length = 667	gi|2827886	35	703	75	81	HCEER84
677	841201			158	571			HCEBD63
678	841202	rhoB [Homo sapiens] >gi|206656 rhoB [Rattus norvegicus] >gnl|PID|e258480 RHOB [Mus musculus] >pir|A01372|TVHURH GTP-binding protein rhoB - human >pir|A39727|TVRTRH GTP-binding protein rhoB - rat >pir|JC5075|JC5075 GTP-binding protein rhoB - mouse >gi|3373	gi|36032	66	1229	100	100	HCHOV21
679	841209			1	552			HCDMF27
680	841210	PTB-associated splicing factor [Homo sapiens] >pir|A46302|A46302 PTB-associated splicing factor, long form - human >gi|23712 myoblast antigen 24.1D5 [Homo sapiens] {SUB 312-707} >gi|4063717 (AF110499) PTB-associated splicing factor [Mus musculus] {SUB 377	gi|38458	2	1405	93	93	HCEMT64

681	841213	G9a [Homo sapiens] >pir|S30385|S30385 G9a protein - human >sp|Q14349|Q14349 G9A PROTEIN CONTAINING ANKYRIN-LIKE REPEATS. Length = 1001	gi|287865	3	344	82	84	HCEFE38
682	841217			2	1198			HCE1V79
683	841219	SMOOTH MUSCLE MYOSIN HEAVY CHAIN (FRAGMENT). Length = 1052	sp|D1037960|D1037960	208	774	95	97	HBZSI02
684	841222			29	856			HCDCI63
685	841223			2088	2486			HCEBW38
686	841224	RNA polymerase II elongation factor ELL2 [Homo sapiens] >sp|O00472|ELL2_HUMAN RNA POLYMERASE II ELONGATION FACTOR ELL2. Length = 640	gi|1946347	2	2032	95	95	HCE2D15
687	841226			2	373			HCCMD50
688	841227			1	831			HBZAK55
689	841228	F25H9.7 [Caenorhabditis elegans] >gnl|PID|e1346003 F25H9.7 [Caenorhabditis elegans] >sp|P91989|P91989 F25H9.7 PROTEIN. Length = 154	gnl|PID|e1346003	3	407	46	62	HCDEA07
690	841231			279	977			HBXCC66

691	841232	MHC HLA-RD protein [Homo sapiens] >pir|A33640|A33640 class III histocompatibility antigen RD - human Length = 382	gi|386949	3	461	94	95	HCE1S91
692	841233	(AF069984) nitrilase homolog 1 [Homo sapiens] >gi|3228666 (AF069987) nitrilase 1 [Homo sapiens] >sp|O76091|O76091 NITRILASE HOMOLOG 1. Length = 327	gi|3242978	2	673	94	95	HBUAF56
693	841234	(AJ005073) Alix [Mus musculus] >sp|O88695|O88695 ALIX. Length = 869	gnl|PID|e1318710	561	2564	89	91	HBWCI70
694	841236			187	483			HBXGB85
695	841238			168	389			HBXFF92
696	841239			405	605			HBMUU08
697	841242			169	360			HBNAT03
698	841243			3	281			HBMTQ45
699	841248	phorbolin 3 [Homo sapiens] >sp|G4097433|G4097433 PHORBOLIN 3. Length = 235	gi|4097433	3	668	46	62	HBUAC02
700	841250			2	1309			HBJEC31
701	841251			5	247			HBJLL24
702	841254			879	1136			HBZSH07
703	841263			1	354			HBJDS57
704	841266			182	337			HBJFN11
705	841269	(AL021958) fadE9 [Mycobacterium tuberculosis] >sp|O53815|O53815 ACYL-COA DEHYDROGENASE. Length = 390	gnl|PID|e1253290	93	1130	51	70	HBDAC79
706	841272	p67 myc protein [Homo sapiens] >sp|D1001846|D1001846 P67 MYC PROTEIN (FRAGMENT). Length = 454	gnl|PID|d1001846	20	622	100	100	HBJFJ36
707	841273			697	948			HBFMD57
708	841276			244	423			HBNAE62

709	841277	NADH-UBIQUINONE OXIDOREDUCTASE 39 KD SUBUNIT PRECURSOR (EC 1.6.5.3) (EC 1.6.99.3) (COMPLEX I-39KD) (CI-39KD). >gi|189049 NADH dehydrogenase (ubiquinone) [Homo sapiens] {SUB 3-377} Length = 377	sp|Q16795|NUEM_HUMAN	2	1171	94	94	HBICG75
710	841278	gag polyprotein - human endogenous virus S71 Length = 608	pir|A46312|A46312	119	415	44	56	HATDB46
711	841279			187	645			HPIAF81
712	841280	(AF061513) candidate adaptor protein CED-6 [Caenorhabditis elegans] >sp|O76337|O76337 CANDIDATE ADAPTOR PROTEIN CED-6. Length = 492	gi|3253308	888	1823	50	69	HBCAS37
713	841282			219	368			HATAM48
714	841283			2530	2880			HBAFS89
715	841286	(AC003096) putative protein phosphatase 2C [Arabidopsis thaliana] >sp|O64583|O64583 HYPOTHETICAL 26.4 KD PROTEIN. Length = 239	gi|3132471	201	1319	57	80	HAHCP59
716	841287			3	248			HARMV18
717	841288	(AL021428) hypothetical protein Rv0068 [Mycobacterium tuberculosis] >sp|O53613|O53613 OXIDOREDUCTASE. Length = 303	gnl|PID|e1245998	3	821			HARMM85
718	841291	selenoprotein P [Homo sapiens] Length = 381	gnl|PID|e1192260	293	1012	88	89	HBMCL13
719	841292	SSR gamma subunit [Rattus norvegicus] >pir|S33294|S33294 translocon-associated protein gamma chain - rat Length = 185	gi|312702	2	664	98	98	HARAI52
720	841294	microtubule associated protein [Homo sapiens] >pir|I37356|I37356 epithelial microtubule-associated protein, 115K - human >sp|Q14244|Q14244 MICROTUBULE ASSOCIATED PROTEIN. Length = 749	gi|414115	3	1265	99	99	HAPOR25

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<tr><td>721</td><td>841296</td><td>protein disulfide isomerase-related protein [Homo sapiens] >pir|A23723|A23723 protein disulfide-isomerase (EC 5.3.4.1) ERp72 precursor - human >sp|P13667|ER72_HUMAN PROTEIN DISULFIDE ISOMERASE-RELATED PROTEIN PRECURSOR (ERP72). Length = 645</td><td>gi|181508</td><td>2</td><td>1405</td><td>96</td><td>96</td><td>HASAS34</td></tr>
<tr><td>722</td><td>841298</td><td>Gps1 [Homo sapiens] >pir|G01646|G01646 Gps1 - human >sp|Q13098|GPS1_HUMAN G PROTEIN PATHWAY SUPPRESSOR 1 (GPS1 PROTEIN) (MFH PROTEIN). {SUB 30-500} Length = 500</td><td>gi|644879</td><td>3</td><td>1067</td><td>91</td><td>91</td><td>HATAI49</td></tr>
<tr><td>723</td><td>841301</td><td></td><td></td><td>10</td><td>231</td><td></td><td></td><td>HAPNO69</td></tr>
<tr><td>724</td><td>841303</td><td>synexin [Homo sapiens] >sp|P20073|ANX7_HUMAN ANNEXIN VII (SYNEXIN). Length = 466</td><td>gi|338244</td><td>3</td><td>1457</td><td>100</td><td>100</td><td>HAOMG39</td></tr>
<tr><td>725</td><td>841304</td><td>(AB000199) CCA2 protein [Rattus norvegicus] >sp|O35048|O35048 CCA2 PROTEIN. Length = 338</td><td>dbj||AB000199_1</td><td>3</td><td>707</td><td>89</td><td>95</td><td>HAPOE40</td></tr>
<tr><td>726</td><td>841305</td><td></td><td></td><td>399</td><td>1274</td><td></td><td></td><td>HAMHD70</td></tr>
<tr><td>727</td><td>841309</td><td>similar to RNA binding protein; >sp|Q19706|IF35_CAEEL PROBABLE EUKARYOTIC TRANSLATION INITIATION FACTOR 3 RNA-BINDING SUBUNIT (EIF-3 RNA-BINDING SUBUNIT) (EIF3 P33) (TRANSLATION INITIATION F</td><td>gnl|PID|e1345859</td><td>137</td><td>1699</td><td>48</td><td>63</td><td>HAPAJ60</td></tr>
<tr><td>728</td><td>841314</td><td></td><td></td><td>3</td><td>920</td><td></td><td></td><td>HAMGN09</td></tr>
<tr><td>729</td><td>841316</td><td>(AJ224819) tumor suppressor [Homo sapiens] >sp|O60858|O60858 TUMOR SUPPRESSOR. Length = 407</td><td>gnl|PID|e1292742</td><td>185</td><td>1420</td><td>93</td><td>93</td><td>HAJCP55</td></tr>
</table>

730	841318	replication control protein 1 [Homo sapiens] >pir|G02329|G02329 replication control protein 1 - human >sp|Q13471|Q13471 REPLICATION CONTROL PROTEIN 1. Length = 861	gi|1171204	170	436	100	100	HAMFQ80
731	841321	hnRNP A2 protein [Homo sapiens] >gnl|PID|d1006583 hnRNP A2 protein [Homo sapiens] >gi|500638 hnRNP protein A2 [Homo sapiens] Length = 341	gi|337449	3	656	100	100	HBJMK69
732	841324	chimeric IFNalpha/beta-receptor [Homo sapiens] >gi|306914 interferon-alpha receptor precursor [Homo sapiens] >pir|A32694|A32694 interferon alpha receptor precursor - human >sp|P17181|INR1_HUMAN INTERFERON-ALPHA/BETA RECEPTOR ALPHA CHAIN PRECURSOR (IFN-ALP	gnl|PID|e251628	31	1755	99	99	HAMGF04
733	841326	Rch1 [Homo sapiens] >gi|899539 hSRP1alpha [Homo sapiens] >pir|A56516|A56516 nuclear localization sequence receptor SRP1 alpha - human >sp|P52292|IMA2_HUMAN IMPORTIN ALPHA-2 SUBUNIT (KARYOPHERIN ALPHA-2 SUBUNIT) (SRP1-ALPHA) (RAG COHORT PROTEIN 1). Length	gi|791185	3	1715	97	97	HAMFV20
734	841328	nuclear ribonucleoprotein [Homo sapiens] >gi|35772 polypirimidine tract binding protein [Homo sapiens] >pir|S26294|S26294 polypyrimidine tract-binding protein - human Length = 557	gi|32354	2	1126	89	89	HAMGF52
735	841329	dJ434P1.3 [Homo sapiens] >gi|1592565 DEAD-box protein p72 [Homo sapiens] >pir|S72367|S72367 ATP-dependent RNA helicase - human >sp|Q92841|P72_HUMAN PROBABLE RNA-DEPENDENT HELICASE P72 (DEAD-BOX PROTEIN P72). Length = 650	gnl|PID|e1249592	93	671	100	100	HAJBV54

		P72 (DEAD-BOX PROTEIN P72). Length = 650						
736	841330	(AF002228) tbx3 [Homo sapiens] >sp|O15119|O15119 TBX3 (FRAGMENT). Length = 468	gi|3041821	3	1097	91	91	HAJAZ71
737	841333	(AB010882) hSNF2H [Homo sapiens] >sp|O60264|O60264 HSNF2H. Length = 1052	gnl|PID|d1026101	1	2004	92	92	HAJBA64
738	841334	SDF2 [Mus musculus] >pir|JC5105|JC5105 stromal cell-derived factor 2 - mouse >sp|P97307|P97307 STROMAL CELL DERIVED FACTOR 2 (SDF2). Length = 211	gnl|PID|d1009954	3	713	59	71	HAJBE68
739	841335			443	946			HAJAT72
740	841336			1	1557			HAJCD33
741	841337			263	1375			HAJAO95
742	841339	transcription factor SC1 [Homo sapiens] >sp|Q13176|Q13176 TRANSCRIPTION FACTOR SC1. Length = 359	gi|833833	27	740	88	89	HAJCB95
743	841340			820	1017			HAJAD20
744	841341			3	359			HAJAL18
745	841342			1145	1417			HAJAI64
746	841343	cellular nucleic acid binding protein [Mus musculus] >pir|I49259|I49259 cellular nucleic acid binding protein - mouse Length = 178	gi|854675	263	685	100	100	HAMGG35
747	841347	(AF038844) MKP-1 like protein tyrosine phosphatase [Homo sapiens] >sp|G4104681|G4104681 MKP-1 LIKE PROTEIN TYROSINE PHOSPHATASE. Length = 198	gi|4104681	161	409	100	100	HAHSE21

748	841352	ribosomal protein L35 [Homo sapiens] >pir|G01477|G01477 ribosomal protein L35 - human Length = 123	gi|562074	3	461	100	100	HBJJF14
749	841353			73	462			HAICO69
750	841354			115	630			HAPNQ64
751	841360			1	816			HAMFM60
752	841366	FKBP65 binding protein [Mus musculus] >pir|I49669|I49669 FKBP65 binding protein - mouse >sp|Q61576|Q61576 FK506 BINDING PROTEIN 6 (65 KDA) (FKBP65 BINDING PROTEIN). Length = 581	gi|894162	222	1319	92	96	HAMGA45
753	841405	cathepsin O [Homo sapiens] >gi|562757 Cathepsin O [Homo sapiens] >bbs|172248 cathepsin O2 [human, spleen, Peptide, 329 aa] [Homo sapiens] >pir|JC2476|JC2476 cathepsin K (EC 3.4.22.-) precursor - human	gi|606923	24	1106	100	100	HOABW85
754	841526	signal recognition particle receptor beta subunit [Mus musculus] >pir|A56487|A56487 signal recognition particle receptor beta chain - mouse Length = 269	gi|600886	3	848	86	88	HABAD39
755	841712			3	698			HBJJT93
756	841860			1984	2352			HPIAP58
757	842042	DNA-binding protein [Homo sapiens] >pir|S69501|S69501 DNA-binding protein A variant - human >sp|Q14121|Q14121 DNA-BINDING PROTEIN. Length = 372	gnl|PID|e219699	2	817	76	76	HBMXV50
758	842453	mitochondrial ATPase inhibitor [Rattus norvegicus] >gnl|PID|d1002924 ATPase inhibitor protein precursor [Rattus sp.] >pir|JS0738|JS0738 ATPase inhibitor protein precursor, mitochondrial - rat >sp|Q03344|IATP_RAT ATPASE INHIBITOR, MITOCHONDRIAL PRECURSOR	gi|517226	13	276	76	88	HBKDV52

PRECURSOR.

759	842635			268	936			HFIIH20
760	842927			2	1630			HCE3G66
761	842988			940	1152			HOSAB76
762	843080			2050	2442			HDPBA08
763	843237			370	1359			HETIJ27
764	843381			520	777			HSIGN74
765	843718	(AF010313) Pig8 [Homo sapiens] >sp|O14681|O14681 PIG8. Length = 318	gi|2415302	212	262	100	100	HMEGI84
766	843823			2	1414			HHESF85
767	844056	(AF010187) FGF-1 intracellular binding protein [Homo sapiens] >gi|2738522 (AF010188) FGF-1 intracellular binding protein [Cercopithecus aethiops] >gi|2738520 (AF010187) FGF-1 intracellular binding protein [Homo sapiens] >gi|2738522 (AF010188) FGF-1 intrac	gi|2738520	2	751	100	100	HE8UZ38
768	844325	(AF059569) actin binding protein MAYVEN [Homo sapiens] >sp|G3789797|G3789797 ACTIN BINDING PROTEIN MAYVEN. Length = 593	gi|3789797	46	1056	37	61	HPRSB90
769	844344	heparin-binding fibroblast growth factor receptor 2 [Rattus norvegicus] >sp|Q63241|Q63241 HEPARIN-BINDING FIBROBLAST GROWTH FACTOR RECEPTOR 2 (FRAGMENT). {SUB 1-330} Length = 331	gi|310149	1	303	40	60	HBJNC37
770	844368	15 KDA SELENOPROTEIN. Length = 162	sp|O60613|O60613	3	374	91	91	HAGHY70

771	844408	(AF001437) dihydrolipoamide dehydrogenase-binding protein [Homo sapiens] Length = 501	gi|2316040	1358	1651	100	100	HTNAD87
772	844508			1	300			HADGG65
773	844867			174	371			HMVBJ82
774	845000			1	321			HE9DB89
775	845281	pre-pro polypeptide (AA -25 to 451) [Homo sapiens] >pir|S09489|S09489 carboxypeptidase H (EC 3.4.17.10) precursor - human >sp|P16870|CBPH_HUMAN CARBOXYPEPTIDASE H PRECURSOR (EC 3.4.17.10) (CPH) (CARBOXYPEPTIDASE E) (CPE) (ENKEPHALIN CONVERTASE) (PROHORMON	gi|29667	3	1475	100	100	HEGAE94
776	845288	(AF023268) propin1 [Homo sapiens] Length = 347	gi|2564915	571	1107	75	76	HTLDM37
777	845750	selenium-binding protein [Homo sapiens] >pir|G01872|G01872 selenium-binding protein - human >sp|Q13228|Q13228 SELENIUM-BINDING PROTEIN. Length = 472	gi|1374792	3	1499	95	96	HE9DH28
778	845809	SNAP23A protein [Homo sapiens] >gnl|PID|e1331767 (AJ011915) synaptosome associated protein of 23 kilodaltons, isoform A [Homo sapiens] >pir|JC5296|JC5296 vesicle-membrane fusion protein SNAP-23A - human >sp|O00161|O00161 VESICLE-MEMBRANE FUSION PROTEIN SN	gnl|PID|e290695	134	772	100	100	HRGSE41
779	846077			182	487			HCNCN11
780	HPFCH77R			21	80			HPFCH77
781	HPRTI05R			2	151			HPRTI05
782	HMSKI93R			25	192			HMSKI93

<table>
<tr><td>783</td><td>HKAAC88R</td><td>(AB003103) 26S proteasome subunit p55 [Homo sapiens] >sp|O00232|O00232 PROTEASOME SUBUNIT P55. Length = 456</td><td>gnl|PID|d1020530</td><td>1</td><td>333</td><td>85</td><td>88</td><td>HKAAC88</td></tr>
<tr><td>784</td><td>HPDED94R</td><td>(AF001212) 26S proteasome subunit 9 [Homo sapiens] >sp|O00495|O00495 26S PROTEASOME SUBUNIT 9. Length = 422</td><td>gi|2150046</td><td>1</td><td>225</td><td>98</td><td>98</td><td>HPDED94</td></tr>
<tr><td>785</td><td>HDTGH11R</td><td>(AF009674) axin [Homo sapiens] >sp|O15169|O15169 AXIN (FRAGMENT). Length = 900</td><td>gi|2252820</td><td>1</td><td>189</td><td>96</td><td>96</td><td>HDTGH11</td></tr>
<tr><td>786</td><td>HTEJR60R</td><td>(AF022184) EZF [Homo sapiens] >sp|O43474|EZF_HUMAN EPITHELIAL ZINC-FINGER PROTEIN EZF. Length = 470</td><td>gi|2897954</td><td>2</td><td>511</td><td>77</td><td>77</td><td>HTEJR60</td></tr>
<tr><td>787</td><td>HAGGY86R</td><td>(AF029786) GBAS [Homo sapiens] >sp|O75323|O75323 GBAS. Length = 286</td><td>gi|3403167</td><td>2</td><td>295</td><td>97</td><td>98</td><td>HAGGY86</td></tr>
<tr><td>788</td><td>HPIAU47R</td><td>(AF031647) JAB1-containing signalosome subunit 3 [Homo sapiens] >sp|O43191|O43191 SIGNALOSOME SUBUNIT 3. Length = 403</td><td>gi|2688989</td><td>3</td><td>377</td><td>89</td><td>91</td><td>HPIAU47</td></tr>
<tr><td>789</td><td>HCGAD89R</td><td>(AF074935) beta-tubulin [Cryptosporidium parvum] >gi|3328337 (AF074936) beta-tubulin [Cryptosporidium parvum] >sp|O77467|O77467 BETA-TUBULIN (FRAGMENT). Length = 57</td><td>gi|3328335</td><td>226</td><td>390</td><td>86</td><td>89</td><td>HCGAD89</td></tr>
<tr><td>790</td><td>HAPOD39R</td><td>(AF089866) keratin 19 [Rattus norvegicus] >sp|G3766220|G3766220 KERATIN 19 (FRAGMENT). Length = 123</td><td>gi|3766220</td><td>3</td><td>386</td><td>88</td><td>93</td><td>HAPOD39</td></tr>
<tr><td>791</td><td>HOGAA68R</td><td>5' half of the product is homologues to Bacillus subtiis SAICAR synthetase, 3' half corresponds to the catalytic subunit of AIR carboxylase [Homo sapiens] >pir|S14147|S14147 multifunctional purine biosynthesis protein - human Length = 425</td><td>gi|28384</td><td>1</td><td>468</td><td>95</td><td>97</td><td>HOGAA68</td></tr>
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792	HCLBO46R	Actin [Drosophila melanogaster] >pir|S14851|S14851 actin - fruit fly (Drosophila melanogaster) >sp|Q24228|Q24228 ACTIN. Length = 100	gi|7550	1	303	94	95	HCLBO46
793	HDRAA14R	ADP,ATP carrier protein T2 - human >sp|P12236|ADT3_HUMAN ADP,ATP CARRIER PROTEIN, LIVER ISOFORM T2 (ADP/ATP TRANSLOCASE 3) (ADENINE NUCLEOTIDE TRANSLOCATOR 3) (ANT 3). Length = 298	pir|S03894|S03894	2	304	80	92	HDRAA14
794	HSLCA48R	alpha-1 (III) collagen [Homo sapiens] Length = 1078	gi|930045	2	457	70	75	HSLCA48
795	HMEAC81R	alpha-subunit of G-protein, type G-alpha-i-1 [Xenopus laevis] >pir|S11045|RGXLI1 GTP-binding regulatory protein Gi alpha-1 chain (adenylate cyclase-inhibiting) - African clawed frog >sp|P27044|GBI1_XENLA GUANINE NUCLEOTIDE-BINDING PROTEIN G(I), ALPHA-1 SU	gi|64708	99	176	92	92	HMEAC81
796	HMQDF20R	beta-1,2-N-acetylglucosaminyltransferase II [Homo sapiens] >pir|S66256|S66256 alpha-1,6-mannosyl-glycoprotein beta-1, 2-N-acetylglucosaminyltransferase (EC 2.4.1.143) - human >sp|Q10469|GNT2_HUMAN ALPHA-1,6-MANNOSYL-GLYCOPROTEIN BETA-1,2-N- ACETYLGLUCOSAM	gi|902745	3	287	85	85	HMQDF20
797	HCHOH06R			12	242			HCHOH06
798	HDQMC20R			3	167			HDQMC20
799	HMKCW11R			2	112			HMKCW11

800	HLDRN91R	C4b-binding protein alpha chain [Homo sapiens] >gi|190502 C4b-binding protein alpha chain [Homo sapiens] >pir|A33568|NBHUC4 C4b-binding protein alpha chain precursor - human >sp|P04003|C4BP_HUMAN C4B-BINDING PROTEIN ALPHA CHAIN PRECURSOR (PROLINE-RICH PRO	gi|190500	2	331	99	100	HLDRN91
801	HCHBR17R	cathepsin D [Homo sapiens] >gi|29678 precursor polypeptide (AA -20 to 392) [Homo sapiens] >gi|181180 preprocathepsin D [Homo sapiens] >pir|A25771|KHHUD cathepsin D (EC 3.4.23.5) precursor - human >sp|P07339|CATD_HUMAN CATHEPSIN D PRECURSOR (EC 3.4.23.5).	gi|179948	3	149	92	92	HCHBR17
802	HMKCH15R	Cbf5p homolog [Homo sapiens] Length = 514	gi|2737894	131	400	81	81	HMKCH15
803	HE6GO78R	clathrin light-chain A [Homo sapiens] Length = 218	gi|307118	155	502	80	83	HE6GO78
804	HSLFI56R	complement component C3 [Homo sapiens] >pir|A94065|C3HU complement C3 precursor - human >sp|P01024|CO3_HUMAN COMPLEMENT C3 PRECURSOR [CONTAINS: C3A ANAPHYLATOXIN]. >gi|181130 complement component C3 [Homo sapiens] {SUB 1-24} Length = 1663	gi|179665	48	422	80	82	HSLFI56
805	HSYBY17R	cyclin G [Homo sapiens] >gi|1236233 cyclin G1 [Homo sapiens] >gi|1236913 cyclin G1 [Homo sapiens] >pir|G02401|G02401 cyclin G1 - human >sp|P51959|CG2G_HUMAN G2/MITOTIC-SPECIFIC CYCLIN G1. >gnl|PID|d1013694 cyclin G [Homo sapiens] {SUB 1-279} >gi|1486361 c	gnl|PID|d1012016	79	300	100	100	HSYBY17

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<tr><td>806</td><td>HPJCS07R</td><td>cytochrome oxidase I [Apteryx australis] >sp|O03515|COX1_APTAU CYTOCHROME C OXIDASE POLYPEPTIDE I (EC 1.9.3.1) (FRAGMENT). Length = 337</td><td>gi|2198683</td><td>113</td><td>226</td><td>83</td><td>92</td><td>HPJCS07</td></tr>
<tr><td>807</td><td>HFADV82R</td><td>cytochrome oxidase III [Homo sapiens] >pir|A00482|OTHU3 cytochrome-c oxidase (EC 1.9.3.1) chain III - human mitochondrion (SGC1) >sp|P00414|COX3_HUMAN CYTOCHROME C OXIDASE POLYPEPTIDE III (EC 1.9.3.1). >gi|2245564 (AF004341) cytochrome c oxidase subunit I</td><td>gi|13010</td><td>1</td><td>105</td><td>81</td><td>83</td><td>HFADV82</td></tr>
<tr><td>808</td><td>HFKFH08R</td><td>DNA polymerase delta small subunit [Homo sapiens] >pir|I38950|I38950 DNA-directed DNA polymerase (EC 2.7.7.7) delta regulatory chain - human >sp|P49005|DPD_HUMAN DNA POLYMERASE DELTA SMALL SUBUNIT (EC 2.7.7.7). Length = 469</td><td>gi|1008458</td><td>2</td><td>550</td><td>97</td><td>98</td><td>HFKFH08</td></tr>
<tr><td>809</td><td>HMCDK47R</td><td>electron transport flavoprotein [Homo sapiens] >pir|A31998|A31998 electron transfer flavoprotein alpha chain precursor - human >sp|P13804|ETFA_HUMAN ELECTRON TRANSFER FLAVOPROTEIN ALPHA-SUBUNIT PRECURSOR (ALPHA-ETF). >gnl|PID|e1331769 (AJ224002) electron</td><td>gi|182251</td><td>3</td><td>320</td><td>100</td><td>100</td><td>HMCDK47</td></tr>
<tr><td>810</td><td>HPIBI27R</td><td>elongation factor 2 [Homo sapiens] >gi|31108 human elongation factor 2 [Homo sapiens] >pir|S18294|EFHU2 translation elongation factor eEF-2 - human >sp|P13639|EF2_HUMAN ELONGATION FACTOR 2 (EF-2). >gi|181969 elongation factor 2 [Homo sapiens] {SUB 501-858</td><td>gi|31106</td><td>23</td><td>319</td><td>98</td><td>98</td><td>HPIBI27</td></tr>
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811	HSKJG37R	elongation factor 2 [Homo sapiens] >gi|31108 human elongation factor 2 [Homo sapiens] >pir|S18294|EFHU2 translation elongation factor eEF-2 - human >sp|P13639|EF2_HUMAN ELONGATION FACTOR 2 (EF-2). >gi|181969 elongation factor 2 [Homo sapiens] {SUB 501-858	gi|31106	1	372	100	100	HSKJG37
812	H2LAZ24R	elongation factor-1-beta [Homo sapiens] >gi|31135 elongation factor 1-beta [Homo sapiens] >pir|S25432|S25432 translation elongation factor eEF-1 beta chain - human >sp|P24534|EF1B_HUMAN ELONGATION FACTOR 1-BETA (EF-1-BETA). {SUB 2-225} Length = 225	gi|31100	23	562	100	100	H2LAZ24
813	H2LAC50R	enhancer protein [Homo sapiens] >pir|I54533|I54533 enhancer protein - human Length = 199	gi|440306	38	415	100	100	H2LAC50
814	HPEAE15R	GLANDULAR KALLIKREIN-1. Length = 223	sp|Q15946|Q15946	51	236	80	80	HPEAE15
815	HPIAA24R	GTP-binding protein Ran/TC4 - mouse (fragment) Length = 70	pir|JH0654|JH0654	382	507	91	91	HPIAA24
816	H2LAS11R	guanylate cyclase (EC 4.6.1.2) - bovine (fragment) >gi|407777 guanylate cyclase [Bos taurus] {SUB 2-498} Length = 498	pir|S48119|S48119	28	549	100	100	H2LAS11
817	HHERW66R	HMG1 protein (AA 1 - 215) [Bos taurus] >pir|S01947|S01947 nonhistone chromosomal protein HMG-1 - bovine >sp|P10103|HMG1_BOVIN HIGH MOBILITY GROUP PROTEIN HMG1 (HMG-1). {SUB 2-215} Length = 215	gi|417	3	386	83	83	HHERW66

818	HADMC73R	hMn-superoxiddismutase [unidentified] >gi|491292 hMN-superoxiddismutase [unidentified] >gnl|PID|e93456 Mn-superoxiddismutase [Homo sapiens] {SUB 23-199} Length = 199	gi|491290	2	94	96	100	HADMC73
819	H6EEU22R	hormone receptor hERR1 (AA 1-521) [Homo sapiens] >pir|A29345|A29345 steroid hormone receptor ERR1 precursor - human >sp|P11474|ERR1_HUMAN STEROID HORMONE RECEPTOR ERR1 (ESTROGEN-RELATED RECEPTOR, ALPHA) (ESTROGEN RECEPTOR-LIKE 1). Length = 521	gi|36609	34	225	100	100	H6EEU22
820	HDTDX66R	HP1Hs-gamma [Homo sapiens] >sp|Q13185|HP1G_HUMAN HETEROCHROMATIN PROTEIN 1 HOMOLOG GAMMA (HP1 GAMMA) (MODIFIER 2 PROTEIN). >sp|G1773227|G1773227 HP1HS-GAMMA. Length = 173	gi|1773227	132	449	82	84	HDTDX66
821	HLPBB39R	human metallothionein-Ie [Homo sapiens] >pir|A22634|SMHU1E metallothionein 1E - human >sp|P04732|MT1E_HUMAN METALLOTHIONEIN-IE (MT-1E). >bbs|144157 metallothionein MT-1e isoform, metallothionein-1e [human, monocytes, Peptide Partial, 31 aa] [Homo sapiens]	gi|386865	40	246	100	100	HLPBB39
822	HOELG04R	hypothetical 18K protein (rRNA) - goldfish mitochondrion (SGC1) Length = 166	pir|JC1348|JC1348	293	415	65	68	HOELG04

823	HKABU38R	initation factor 4B [Homo sapiens] >pir|S12566|S12566 translation initiation factor eIF-4B - human >sp|P23588|IF4B_HUMAN EUKARYOTIC TRANSLATION INITIATION FACTOR 4B (EIF-4B). Length = 611	gi|288100	2	463	92	92	HKABU38
824	HBGOI32R	keratin 18 [Homo sapiens] >gi|307081 keratin 18 precursor [Homo sapiens] >gi|34037 cytokeratin 18 [Homo sapiens] >pir|S05481|S05481 keratin 18, type I, cytoskeletal - human >sp|P05783|K1CR_HUMAN KERATIN, TYPE I CYTOSKELETAL 18 (CYTOKERATIN 18) (K18) (CK 1	gi|386844	1	240	66	67	HBGOI32
825	HATAI03R	KIAA0106 [Homo sapiens] >sp|P30041|AOP2_HUMAN ANTIOXIDANT PROTEIN 2 (EC 1.11.1.7) (24 KD PROTEIN) (LIVER 2D PAGE SPOT 40) (RED BLOOD CELLS PAGE SPOT 12). {SUB 2-224} Length = 224	gnl|PID|d1004007	3	194	90	93	HATAI03
826	HCEDE25R	KIAA0106 [Homo sapiens] >sp|P30041|AOP2_HUMAN ANTIOXIDANT PROTEIN 2 (EC 1.11.1.7) (24 KD PROTEIN) (LIVER 2D PAGE SPOT 40) (RED BLOOD CELLS PAGE SPOT 12). {SUB 2-224} Length = 224	gnl|PID|d1004007	2	283	100	100	HCEDE25
827	HKDBF62R	metallothionein-IG [Homo sapiens] >pir|A29236|SMHU1G metallothionein 1G - human >sp|P13640|MT1G_HUMAN METALLOTHIONEIN-IG (MT-1G). >bbs|144160 metallothionein MT-1g isoform, metallothionein-1g [human, monocytes, Peptide Partial, 31 aa] [Homo sapiens] {SUB	gi|188713	170	322	95	95	HKDBF62

828	HNTSX94R	mitochondrial matrix protein [Homo sapiens] >pir|A32800|A32800 chaperonin GroEL precursor - human >sp|P10809|P60_HUMAN MITOCHONDRIAL MATRIX PROTEIN P1 PRECURSOR (P60 LYMPHOCYTE PROTEIN) (60 KD CHAPERONIN) (HEAT SHOCK PROTEIN 60) (HSP-60) (PROTEIN CPN60) (	gi|190127	3	431	97	100	HNTSX94
829	HRGBR08R	mitochondrial matrix protein [Homo sapiens] >pir|A32800|A32800 chaperonin GroEL precursor - human >sp|P10809|P60_HUMAN MITOCHONDRIAL MATRIX PROTEIN P1 PRECURSOR (P60 LYMPHOCYTE PROTEIN) (60 KD CHAPERONIN) (HEAT SHOCK PROTEIN 60) (HSP-60) (PROTEIN CPN60) (	gi|190127	1	504	94	94	HRGBR08
830	H2LAO77R	MSS1 protein [Homo sapiens] >pir|S24353|S24353 proteasome 26S subunit MSS1 - human >sp|G385267|G385267 26 S PROTEASE SUBUNIT 7, MSS1=MODULATOR OF HIV TAT-MEDIATED TRANSACTIVATION. {SUB 2-23} Length = 433	gnl|PID|d1002345	137	580	91	91	H2LAO77
831	HNTRW15R	NAD+ ADP-ribosyltransferase [Homo sapiens] >pir|A29725|A29725 NAD+ ADP-ribosyltransferase (EC 2.4.2.30), nuclear - human >sp|P09874|PPOL_HUMAN POLY [ADP-RIBOSE] POLYMERASE (EC 2.4.2.30) (PARP) (ADPRT) (NAD(+) ADP-RIBOSYLTRANSFERASE) (POLY[ADP-RIBOSE] SYN	gi|178190	163	297	90	96	HNTRW15

832	HORBH08R	NADH dehydrogenase (ubiquinone) (EC 1.6.5.3) 51K chain precursor - human (fragment) >sp|P49821|NUBM_HUMAN NADH-UBIQUINONE OXIDOREDUCTASE 51 KD SUBUNIT PRECURSOR (EC 1.6.5.3) (EC 1.6.99.3) (COMPLEX I-51KD) (CI-51KD) (FRAGMENT). >bbs|142159 NADH:ubiquinone	pir|A44362|A44362	186	428	83	87	HORBH08
833	HULBL38R	nonstructural protein P125-2 [pestivirus type 1] >sp|O57114|O57114 NONSTRUCTURAL PROTEIN P125-2 (FRAGMENT). Length = 239	gi|2707597	3	437	95	97	HULBL38
834	HNTBK49R	p60 [Homo sapiens] >sp|Q13446|Q13446 EBI3-ASSOCIATED PROTEIN P60. >gi|3283216 (AF060494) ubiquitin binding protein p62 [Homo sapiens] {SUB 1-72} Length = 440	gi|1145799	3	368	100	100	HNTBK49
835	HBAFS48R	Phalaenopsis sp. 'hybrid SM9108' actin [Phalaenopsis sp. 'hybrid SM9108'] >sp|Q40981|Q40981 ACTIN (FRAGMENT). Length = 208	gi|602958	2	316	91	92	HBAFS48
836	HHGAL60R	PIPPin protein [Rattus norvegicus] >pir|JC4588|JC4588 RNA-binding protein PIPPin - rat >sp|Q63430|Q63430 PIPPIN PROTEIN. Length = 154	gi|1050754	2	319	66	81	HHGAL60
837	HOHBU75R	prepro-alpha-1 collagen [Homo sapiens] >sp|Q15201|Q15201 PREPRO-ALPHA-1 COLLAGEN PRECURSOR (FRAGMENT). Length = 181	gi|35658	104	373	71	72	HOHBU75
838	HHEFZ79R	progesterone-induced protein [Oryctolagus cuniculus] >pir|A26998|A26998 progesterone-induced protein, endometrial - rabbit Length = 370	gi|165009	293	484	73	77	HHEFZ79

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<tr><td>839</td><td>HSLBA61R</td><td>proteasome subunit C5 [Homo sapiens] >gnl|PID|e1334433 (AL031259) C5 (proteasome subunit HC5) [Homo sapiens] >pir|S15973|SNHUC5 multicatalytic endopeptidase complex (EC 3.4.99.46) chain C5 - human >sp|P20618|PRC5_HUMAN PROTEASOME COMPONENT C5 (EC 3.4.99.4</td><td>gnl|PID|d1001116</td><td>45</td><td>224</td><td>96</td><td>96</td><td>HSLBA61</td></tr>
<tr><td>840</td><td>HPEAE18R</td><td>put. ORF [Homo sapiens] >pir|I38022|I38022 hypothetical protein - human >sp|Q29976|Q29976 MAHLAVU HEPATOCELLULAR CARCINOMA HHC(M) DNA. Length = 196</td><td>gi|288145</td><td>55</td><td>234</td><td>57</td><td>67</td><td>HPEAE18</td></tr>
<tr><td>841</td><td>HNGFO65R</td><td>ren(exclusion;96) [Bacteriophage lambda] >pir|F43010|ZRBPL ren protein - phage lambda Length = 96</td><td>gi|215152</td><td>3</td><td>203</td><td>48</td><td>59</td><td>HNGFO65</td></tr>
<tr><td>842</td><td>HKAKR61R</td><td>ribosmal protein small subunit [Homo sapiens] Length = 264</td><td>gi|306553</td><td>3</td><td>458</td><td>91</td><td>91</td><td>HKAKR61</td></tr>
<tr><td>843</td><td>H2LAP11R</td><td>ribosomal phosphoprotein P1 (AA 1-114) [Rattus rattus] >pir|S08022|R5RT12 acidic ribosomal protein P1 - rat Length = 114</td><td>gi|57710</td><td>169</td><td>549</td><td>100</td><td>100</td><td>H2LAP11</td></tr>
<tr><td>844</td><td>H2CBD90R</td><td>ribosomal protein L10 [Homo sapiens] >sp|D1026771|D1026771 RIBOSOMAL PROTEIN L15 (FRAGMENT). {SUB 16-57} Length = 205</td><td>gi|414587</td><td>199</td><td>501</td><td>95</td><td>95</td><td>H2CBD90</td></tr>
<tr><td>845</td><td>H2LAD40R</td><td>ribosomal protein L15 gene product [Rattus norvegicus] >pir|JC2369|JC2369 ribosomal protein L15 - rat Length = 204</td><td>gi|515865</td><td>156</td><td>524</td><td>100</td><td>100</td><td>H2LAD40</td></tr>
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<tr><td>846</td><td>HCYBK51R</td><td>ribosomal protein L37 [Homo sapiens] >bbs|172744 ribosomal protein L37 {C2-C2 zinc-finger-like} [human, HeLa cells, Peptide, 97 aa] [Homo sapiens] >gnl|PID|d1005426 ribosomal protein L37 [Homo sapiens] >gi|57121 ribosomal protein L37 [Rattus norvegicus] ></td><td>gi|292441</td><td>2</td><td>412</td><td>97</td><td>98</td><td>HCYBK51</td></tr>
<tr><td>847</td><td>H2MBC73R</td><td>ribosomal protein L37a [Homo sapiens] >gi|36134 ribosomal protein L37a [Homo sapiens] >gi|57123 ribosomal protein L37a (AA 1 - 92) [Rattus rattus] >gi|312414 ribosomal protein L37a [Mus musculus] >pir|S05014|R5RT37 ribosomal protein L37a - rat >pir|S42109</td><td>gi|292439</td><td>2</td><td>385</td><td>100</td><td>100</td><td>H2MBC73</td></tr>
<tr><td>848</td><td>H2MBU27R</td><td>ribosomal protein L37a [Homo sapiens] >gi|36134 ribosomal protein L37a [Homo sapiens] >gi|57123 ribosomal protein L37a (AA 1 - 92) [Rattus rattus] >gi|312414 ribosomal protein L37a [Mus musculus] >pir|S05014|R5RT37 ribosomal protein L37a - rat >pir|S42109</td><td>gi|292439</td><td>2</td><td>286</td><td>100</td><td>100</td><td>H2MBU27</td></tr>
<tr><td>849</td><td>HDSAH53R</td><td>ribosomal protein L37a [Homo sapiens] >gi|36134 ribosomal protein L37a [Homo sapiens] >gi|57123 ribosomal protein L37a (AA 1 - 92) [Rattus rattus] >gi|312414 ribosomal protein L37a [Mus musculus] >pir|S05014|R5RT37 ribosomal protein L37a - rat >pir|S42109</td><td>gi|292439</td><td>3</td><td>341</td><td>97</td><td>97</td><td>HDSAH53</td></tr>
<tr><td>850</td><td>HAIDF69R</td><td>ribosomal protein L7a [Fugu rubripes] Length = 266</td><td>gnl|PID|e1248480</td><td>179</td><td>250</td><td>93</td><td>100</td><td>HAIDF69</td></tr>
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851	HDBAA15R	ribosomal protein L8 [Homo sapiens] >gi|57704 ribosomal protein L8 [Rattus rattus] >gi|1527178 ribosomal protein L8 [Mus musculus] >pir|JU0177|R5RTL8 ribosomal protein L8, cytosolic - rat >pir|JN0923|JN0923 ribosomal protein L8, cytosolic - human >gi|3851	gi|433899	220	429	85	88	HDBAA15
852	HDTHW54R	ribosomal protein S12 (AA 1 - 132) [Mus musculus] >pir|S13074|R3RT12 ribosomal protein S12 - rat >pir|S05492|R3MS12 ribosomal protein S12 - mouse >gi|206741 ribosomal protein S12 [Rattus norvegicus] {SUB 1-130} Length = 132	gi|54006	3	332	89	89	HDTHW54
853	HTWJC11R	ribosomal protein S13 [Homo sapiens] >gi|488417 ribosomal protein S13 [Homo sapiens] >gnl|PID|d1014222 ribosomal protein S13 [Homo sapiens] >gi|57730 ribosomal protein S13 [Rattus rattus] >pir|S34109|S34109 ribosomal protein S13, cytosolic - human >pir|A3	gi|307391	1	276	97	97	HTWJC11
854	HKAEC40R	ribosomal protein S24 [Homo sapiens] >gi|517222 ribosomal protein S24 [Homo sapiens] >gi|49652 ribosomal protein S19 (AA 1 - 133) [Mesocricetus auratus] >gi|57858 ribosomal protein S24 [Rattus norvegicus] >gi|57722 ribosomal protein S24 (AA 1-133) [Rattus	gi|337506	93	407	83	84	HKAEC40
855	HCFNM70R	ribosomal protein S4X isoform [Homo sapiens] >gi|2791861 (AF041428) ribosomal protein s4 X isoform [Homo sapiens] >gi|200864 ribosomal protein S4 [Mus musculus] >gi|57135 ribosomal protein S4 (AA 1 - 263) [Rattus rattus] >gnl|PID|d1002335 ribosomal protei	gi|337510	3	278	96	97	HCFNM70

856	HKBAB93R	ribosomal protein S8 [Homo sapiens] >gi|57139 ribosomal protein S8 (AA 1-208) [Rattus norvegicus] >gi|313298 ribosomal protein S8 [Mus musculus] >pir|S01609|R3RT8 ribosomal protein S8 - rat >pir|S42110|S42110 ribosomal protein S8 - mouse >pir|S25022|S2502	gi|36150	2	391	87	90	HKBAB93
857	HLHEJ79R	RNA polymerase II subunit hRPB17 [Homo sapiens] >pir|S55370|S55370 RNA polymerase II chain hRPB17 - human Length = 150	gi|854177	129	446	83	86	HLHEJ79
858	HBGOI24R	S19 ribosomal protein [Homo sapiens] >pir|I52692|I52692 ribosomal protein S19, cytosolic - human Length = 145	gi|337733	2	421	99	100	HBGOI24
859	HNDAD16R	secretory protein [Homo sapiens] >gi|940946 intestinal trefoil factor [Homo sapiens] >pir|A48284|A48284 intestinal trefoil factor 3 precursor - human >sp|Q07654|ITF_HUMAN INTESTINAL TREFOIL FACTOR PRECURSOR (HP1.B). Length = 80	gi|402483	3	380	71	78	HNDAD16
860	HMAEA94R	serine/threonine protein kinase [Homo sapiens] >gnl|PID|e1154172 (AJ000512) serine/threonine protein kinase [Homo sapiens] Length = 431	gnl|PID|e293330	3	422	95	95	HMAEA94
861	HMWEA08R	signal recognition particle subunit 9 [Homo sapiens] >pir|A57292|A57292 signal recognition particle protein SRP9 - human Length = 86	gi|897851	119	394	90	93	HMWEA08
862	H6BSO48R	similar to Drosophila photoreceptor cell-specific protein, calphotin. [Homo sapiens] >sp|Q14676|Q14676 KIAA0170 PROTEIN. Length = 2089	gnl|PID|d1012153	1	528	95	95	H6BSO48

863	HRACC09R	smooth muscle protein [Homo sapiens] >pir|JS0774|JS0774 smooth muscle protein SM22 - human Length = 201	gi|177175	1	117	100	100	HRACC09
864	HOEEC67R	smooth muscle protein SM22 homolog - mouse Length = 201	pir|A60598|A60598	105	230	100	100	HOEEC67
865	HPFEA40R	t-complex polypeptide 1 (AA 1-556) [Homo sapiens] Length = 556	gi|36796	3	497	98	99	HPFEA40
866	HODAV31R	tissue inhibitor of metalloproteinases [Homo sapiens] Length = 166	gnl|PID|d1002390	1	273	64	67	HODAV31
867	HHECI89R	transaldolase [Homo sapiens] >gi|2612879 (AF010400) transaldolase-related protein [Homo sapiens] >sp|O00751|O00751 TRANSALDOLASE (EC 2.2.1.2). >gi|1480787 transaldolase [Homo sapiens] {SUB 302-337} Length = 337	gi|2073541	3	371	99	99	HHECI89
868	HSDFV03R	translocase [Bos taurus] >pir|B43646|B43646 ADP,ATP carrier protein T2 - bovine >sp|P32007|ADT3_BOVIN ADP,ATP CARRIER PROTEIN, ISOFORM T2 (ADP/ATP TRANSLOCASE 3) (ADENINE NUCLEOTIDE TRANSLOCATOR 3) (ANT 3). Length = 298	gi|529417	20	412	92	96	HSDFV03
869	HTXPN01R	triose-phosphate isomerase [Pan troglodytes] >gi|37247 triosephosphate isomerase [Homo sapiens] >gi|1200507 triosephosphate isomerase [Homo sapiens] >gi|339841 triosephosphate isomerase (EC 5.3.1.1) [Homo sapiens] >pir|S29743|ISHUT triose-phosphate isomer	gi|176960	3	281	98	98	HTXPN01
870	HHPSA49R	tuberin [Homo sapiens] Length = 1784	gi|450352	2	451	69	69	HHPSA49
871	H2LAT88R	type II mesothelial keratin K7 [Homo sapiens] >sp|Q92676|Q92676 MESOTHELIAL KERATIN K7 (TYPE II) (FRAGMENT). Length = 489	gi|386851	1	567	91	91	H2LAT88

872	H6EAD58R	49	174	H6EAD58
873	HACBH95R	2	364	HACBH95
874	HACBY16R	1	84	HACBY16
875	HAGCI33R	2	238	HAGCI33
876	HAHAD34R	61	123	HAHAD34
877	HAJAN69R	67	294	HAJAN69
878	HALSG52R	41	268	HALSG52
879	HAPPR17R	180	311	HAPPR17
880	HAQCG78R	3	110	HAQCG78
881	HAUBY86R	23	118	HAUBY86
882	HAVAA34R	1	117	HAVAA34
883	HBAFK20R	2	355	HBAFK20
884	HBGBE20R	31	315	HBGBE20
885	HBJBR66R	2	52	HBJBR66
886	HBJMU59R	2	208	HBJMU59
887	HBKDK63R	147	647	HBKDK63
888	HBMVT43R	2	70	HBMVT43
889	HCDAM59R	21	125	HCDAM59
890	HCFLN25R	3	224	HCFLN25
891	HCQAW59R	1	129	HCQAW59
892	HDPMA46R	223	420	HDPMA46
893	HDTAQ26R	177	296	HDTAQ26
894	HDTAT40R	1	213	HDTAT40
895	HDTLD39R	323	496	HDTLD39
896	HE2PO63R	39	278	HE2PO63
897	HELCV09R	1	72	HELCV09
898	HELHK95R	3	383	HELHK95
899	HEMGL70R	2	172	HEMGL70
900	HETIB72R	2	100	HETIB72
901	HFFAS19R	2	256	HFFAS19
902	HFIYH65R	68	259	HFIYH65

903	HFXAF89R	143	361	HFXAF89
904	HHEPR03R	89	307	HHEPR03
905	HHGAQ80R	2	202	HHGAQ80
906	HHSEF82R	170	304	HHSEF82
907	HKBAA63R	239	469	HKBAA63
908	HKIXO47R	2	94	HKIXO47
909	HLDNF70R	3	176	HLDNF70
910	HLQFO33R	62	268	HLQFO33
911	HLWBC80R	46	543	HLWBC80
912	HLYAV50R	3	224	HLYAV50
913	HMEKY67R	3	302	HMEKY67
914	HMTBN58R	3	377	HMTBN58
915	HNGAZ91R	22	276	HNGAZ91
916	HNTAC06R	2	133	HNTAC06
917	HOGAF41R	1	228	HOGAF41
918	HOUDQ92R	75	323	HOUDQ92
919	HPEAD91R	60	233	HPEAD91
920	HPIAF72R	128	310	HPIAF72
921	HPIAU01R	122	334	HPIAU01
922	HPIAU73R	99	275	HPIAU73
923	HPIAW19R	102	350	HPIAW19
924	HPIAZ19R	238	348	HPIAZ19
925	HPIBA31R	245	367	HPIBA31
926	HPIBS06R	84	182	HPIBS06
927	HPICB65R	2	430	HPICB65
928	HPJBF22R	220	330	HPJBF22
929	HPJBZ81R	214	384	HPJBZ81
930	HRACF81R	1	189	HRACF81
931	HRACT28R	110	319	HRACT28
932	HSBAP03R	123	263	HSBAP03
933	HSDJK57R	234	458	HSDJK57

<table>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>934</td><td>HSIFY54R</td><td></td><td></td><td>1</td><td>321</td><td></td><td></td><td>HSIFY54</td></tr>
<tr><td>935</td><td>HSLDJ92R</td><td></td><td></td><td>24</td><td>275</td><td></td><td></td><td>HSLDJ92</td></tr>
<tr><td>936</td><td>HSLJI47R</td><td></td><td></td><td>185</td><td>379</td><td></td><td></td><td>HSLJI47</td></tr>
<tr><td>937</td><td>HTSGE55R</td><td></td><td></td><td>36</td><td>209</td><td></td><td></td><td>HTSGE55</td></tr>
<tr><td>938</td><td>HUFAT72R</td><td></td><td></td><td>276</td><td>410</td><td></td><td></td><td>HUFAT72</td></tr>
<tr><td>939</td><td>HULAI70R</td><td></td><td></td><td>176</td><td>337</td><td></td><td></td><td>HULAI70</td></tr>
<tr><td>940</td><td>HTGFW12R</td><td>yeast mismatch repair gene PMS1 homologue [Homo sapiens] >gnl|PID|d1008050 homologue of yeast PMS1 [Homo sapiens] >sp|Q16530|Q16530 PMS3 MRNA (YEAST MISMATCH REPAIR GENE PMS1 HOMOLOGUE), PARTIAL CDS (C-TERMINAL REGION) (FRAGMENT). Length = 256</td><td>gnl|PID|d1008092</td><td>3</td><td>233</td><td>94</td><td>97</td><td>HTGFW12</td></tr>
</table>

[0039] The first column of Table 1 shows the "SEQ ID NO:" for each of the 940 prostate cancer antigen polynucleotide sequences of the invention.

[0040] The second column in Table 1, provides a unique "Sequence/Contig ID" identification for each prostate and/or prostate cancer associated sequence. The third column in Table 1, "Gene Name," provides a putative identification of the gene based on the sequence similarity of its translation product to an amino acid sequence found in a publicly accessible gene database, such as GenBank (NCBI). The great majority of the cDNA sequences reported in Table 1 are unrelated to any sequences previously described in the literature. The fourth column, in Table 1, "Overlap," provides the database accession no. for the database sequence having similarity. The fifth and sixth columns in Table 1 provide the location (nucleotide position nos. within the contig), "Start" and "End", in the polynucleotide sequence "SEQ ID NO:X" that delineate the preferred ORF shown in the sequence listing as SEQ ID NO:Y. In one embodiment, the invention provides a protein comprising, or alternatively consisting of, a polypeptide encoded by the portion of SEQ ID NO:X delineated by the nucleotide position nos. "Start" and "End". Also provided are polynucleotides encoding such proteins and the complementary strand thereto. The seventh and eighth columns provide the "% Id" (percent identity) and "% Si" (percent similarity) observed between the aligned sequence segments of the translation product of SEQ ID NO:X and the database sequence.

[0041] The ninth column of Table 1 provides a unique "Clone ID" for a clone related to each contig sequence. This clone ID references the cDNA clone which contains at least the 5' most sequence of the assembled contig and at least a portion of SEQ ID NO:X was determined by directly sequencing the referenced clone. The reference clone may have more sequence than described in the sequence listing or the clone may have less. In the vast majority of cases, however, the clone is believed to encode a full-length polypeptide. In the case where a clone is not full-length, a full-length cDNA can be obtained by methods described elsewhere herein.

[0042] Table 3 indicates public ESTs, of which at least one, two, three, four, five, ten, or more of any one or more of these public ESTs are optionally excluded from the invention.

[0043] SEQ ID NO:X (where X may be any of the polynucleotide sequences disclosed in the sequence listing as SEQ ID NO:1 through SEQ ID NO:940) and the

translated SEQ ID NO:Y (where Y may be any of the polypeptide sequences disclosed in the sequence listing as SEQ ID NO:941 through SEQ ID NO:1880) are sufficiently accurate and otherwise suitable for a variety of uses well known in the art and decribed further below. For instance, SEQ ID NO:X has uses including, but not limited to, in designing nucleic acid hybridization probes that will detect nucleic acid sequences contained in SEQ ID NO:X or the related cDNA clone contained in a library deposited with the ATCC. These probes will also hybridize to nucleic acid molecules in biological samples, thereby enabling immediate applications in chromosome mapping, linkage analysis, tissue identification and/or typing, and a variety of forensic and diagnostic methods of the invention. Similarly, polypeptides identified from SEQ ID NO:Y have uses that include, but are not limited to, generating antibodies which bind specifically to the prostate cancer antigen polypeptides, or fragments thereof, and/or to the prostate cancer antigen polypeptides encoded by the cDNA clones identified in Table 1.

[0044] Nevertheless, DNA sequences generated by sequencing reactions can contain sequencing errors. The errors exist as misidentified nucleotides, or as insertions or deletions of nucleotides in the generated DNA sequence. The erroneously inserted or deleted nucleotides cause frame shifts in the reading frames of the predicted amino acid sequence. In these cases, the predicted amino acid sequence diverges from the actual amino acid sequence, even though the generated DNA sequence may be greater than 99.9% identical to the actual DNA sequence (for example, one base insertion or deletion in an open reading frame of over 1000 bases).

[0045] Accordingly, for those applications requiring precision in the nucleotide sequence or the amino acid sequence, the present invention provides not only the generated nucleotide sequence identified as SEQ ID NO:X, the predicted translated amino acid sequence identified as SEQ ID NO:Y, but also a sample of plasmid DNA containing the related cDNA clone (deposited with the ATCC, as set forth in Table 1). The nucleotide sequence of each deposited clone can readily be determined by sequencing the deposited clone in accordance with known methods. Further, techniques known in the art can be used to verify the nucleotide sequences of SEQ ID NO:X.

[0046] The predicted amino acid sequence can then be verified from such deposits. Moreover, the amino acid sequence of the protein encoded by a particular clone can also be directly determined by peptide sequencing or by expressing the protein in a suitable

host cell containing the deposited human cDNA, collecting the protein, and determining its sequence.

[0047] The present invention also relates to vectors or plasmids which include such DNA sequences, as well as the use of the DNA sequences. The material deposited with the ATCC on:

TABLE 2

ATCC Deposits	Deposit Date	ATCC Designation Number
LP01, LP02, LP03, LP04, LP05, LP06, LP07, LP08, LP09, LP10, LP11,	May-20-97	209059, 209060, 209061, 209062, 209063, 209064, 209065, 209066, 209067, 209068, 209069
LP12	Jan-12-98	209579
LP13	Jan-12-98	209578
LP14	Jul-16-98	203067
LP15	Jul-16-98	203068
LP16	Feb-1-99	203609
LP17	Feb-1-99	203610
LP20	Nov-17-98	203485
LP21	Jun-18-99	PTA-252
LP22	Jun-18-99	PTA-253
LP23	Dec-22-99	PTA-1081

each is a mixture of cDNA clones derived from a variety of human tissue and cloned in either a plasmid vector or a phage vector, as shown in Table 5. These deposits are referred to as "the deposits" herein. The tissues from which the clones were derived are listed in Table 5, and the vector in which the cDNA is contained is also indicated in Table 5. The deposited material includes the cDNA clones which were partially sequenced and are related to the SEQ ID NO:X described in Table 1 (column 9). Thus, a clone which is isolatable from the ATCC Deposits by use of a sequence listed as SEQ ID NO:X may include the entire coding region of a human gene or in other cases such clone may include

a substantial portion of the coding region of a human gene. Although the sequence listing lists only a portion of the DNA sequence in a clone included in the ATCC Deposits, it is well within the ability of one skilled in the art to complete the sequence of the DNA included in a clone isolatable from the ATCC Deposits by use of a sequence (or portion thereof) listed in Table 1 by procedures hereinafter further described, and others apparent to those skilled in the art.

[0048] Also provided in Table 5 is the name of the vector which contains the cDNA clone. Each vector is routinely used in the art. The following additional information is provided for convenience.

[0049] Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., *Nucleic Acids Res. 16:*7583-7600 (1988); Alting-Mees, M. A. and Short, J. M., *Nucleic Acids Res. 17:*9494 (1989)) and pBK (Alting-Mees, M. A. et al., *Strategies 5:*58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Phagemid pBS may be excised from the Lambda Zap and Uni-Zap XR vectors, and phagemid pBK may be excised from the Zap Express vector. Both phagemids may be transformed into *E. coli* strain XL-1 Blue, also available from Stratagene.

[0050] Vectors pSport1, pCMVSport 1.0, pCMVSport 2.0 and pCMVSport 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, also available from Life Technologies. See, for instance, Gruber, C. E., et al., *Focus 15:*59 (1993). Vector lafmid BA (Bento Soares, Columbia University, New York, NY) contains an ampicillin resistance gene and can be transformed into *E. coli* strain XL-1 Blue. Vector pCR®2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, available from Life Technologies. See, for instance, Clark, J. M., *Nuc. Acids Res. 16:*9677-9686 (1988) and Mead, D. *et al., Bio/Technology 9:* (1991).

[0051] The present invention also relates to the genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, and/or the cDNA contained in a deposited cDNA clone. The

corresponding gene can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include, but are not limited to, preparing probes or primers from the disclosed sequence and identifying or amplifying the corresponding gene from appropriate sources of genomic material.

[0052] Also provided in the present invention are allelic variants, orthologs, and/or species homologs. Procedures known in the art can be used to obtain full-length genes, allelic variants, splice variants, full-length coding portions, orthologs, and/or species homologs of genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, and/or the cDNA contained in the related cDNA clone in the deposit, using information from the sequences disclosed herein or the clones deposited with the ATCC. For example, allelic variants and/or species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source for allelic variants and/or the desired homologue.

[0053] The present invention provides a polynucleotide comprising, or alternatively consisting of, the nucleic acid sequence of SEQ ID NO:X, and/or the related cDNA clone (See, e.g., columns 1 and 9 of Table 1). The present invention also provides a polypeptide comprising, or alternatively, consisting of, the polypeptide sequence of SEQ ID NO:Y, a polypeptide encoded by SEQ ID NO:X, and/or a polypeptide encoded by the cDNA in the related cDNA clone contained in a deposited library. Polynucleotides encoding a polypeptide comprising, or alternatively consisting of, the polypeptide sequence of SEQ ID NO:Y, a polypeptide encoded by SEQ ID NO:X, and/or a polypeptide encoded by the the dDNA in the related cDNA clone contained in a deposited library, are also encompassed by the invention. The present invention further encompasses a polynucleotide comprising, or alternatively consisting of, the complement of the nucleic acid sequence of SEQ ID NO:X, and/or the complement of the coding strand of the related cDNA clone contained in a deposited library.

[0054] Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would unduly burden the disclosure of this application. Accordingly, for each "Contig Id" listed in the first column of Table 3, preferably excluded are one or more

polynucleotides comprising a nucleotide sequence described in the second column of Table 3 by the general formula of a-b, each of which are uniquely defined for the SEQ ID NO:X corresponding to that Contig Id in Table 1. Additionally, specific embodiments are directed to polynucleotide sequences excluding at least one, two, three, four, five, ten, or more of the specific polynucleotide sequences referenced by the Genbank Accession No. for each Contig Id which may be included in column 3 of Table 3. In no way is this listing meant to encompass all of the sequences which may be excluded by the general formula, it is just a representative example.

TABLE 3

Sequence/ Contig ID	General formula	Genbank Accession No.
574130	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 703 of SEQ ID NO:1, b is an integer of 15 to 717, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:1, and where b is greater than or equal to a + 14.	
637706	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1611 of SEQ ID NO:2, b is an integer of 15 to 1625, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:2, and where b is greater than or equal to a + 14.	
638162	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2421 of SEQ ID NO:3, b is an integer of 15 to 2435, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:3, and where b is greater than or equal to a + 14.	R78923, R79022, H78714, H78726, H79487, H79500, H86682, H99479, N22197, N28292, N48317, N49043, N79526, W16679, AA017524, AA017582, AA215755, AA463914
684310	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 972 of SEQ ID NO:4, b is an integer of 15 to 986, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:4, and where b is greater than or equal to a + 14.	R00703, R79938, R80028, N75501, N99910, W25289
731016	Preferably excluded from the present invention are one or more	

	polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 356 of SEQ ID NO:5, b is an integer of 15 to 370, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:5, and where b is greater than or equal to a + 14.	
827771	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 497 of SEQ ID NO:6, b is an integer of 15 to 511, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:6, and where b is greater than or equal to a + 14.	
828193	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 704 of SEQ ID NO:7, b is an integer of 15 to 718, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:7, and where b is greater than or equal to a + 14.	
828194	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 431 of SEQ ID NO:8, b is an integer of 15 to 445, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:8, and where b is greater than or equal to a + 14.	
828199	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 744 of SEQ ID NO:9, b is an integer of 15 to 758, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:9, and where b is greater than or equal to a + 14.	
828221	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3050 of SEQ ID NO:10, b is an integer of 15 to 3064, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:10, and where b is greater than or equal to a + 14.	T47410, T54389, T54694, T47411, T54281, T54610, T58617, T58667, T78082, T78249, T80561, R28515, R28663, R38862, R54617, R54880, H08112, H08113, H16261, H16460, H22343, H22344, H29551, H29643, H41933, H41980, R83220, R83221, R85675, R89016, R89017, R99602, R99707, H58947, H58994, H59578, H59579, H62419, H91312, H91409, N54589, N66610,

		N73945, N76670, W03705, W04654, W31578, W38370, W39449, W93512, W93513, AA024819, AA024925, AA033860, AA076628, AA159000, AA193455, AA257006, AA225275, AA483288, AA507139, AA522771, AA527181, AA534997, AA541666, AA614359, AA614596, AA622977, AA622978, AA569985, AA576092, AA659398, AA826776, AA836985, AA864814, AA904006, AA911931, AA916611, AA932076, AA991541, C06189
828235	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1482 of SEQ ID NO:11, b is an integer of 15 to 1496, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:11, and where b is greater than or equal to a + 14.	AA045157, AA252563, AA573229, AA935280
828236	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1413 of SEQ ID NO:12, b is an integer of 15 to 1427, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:12, and where b is greater than or equal to a + 14.	
828237	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3534 of SEQ ID NO:13, b is an integer of 15 to 3548, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:13, and where b is greater than or equal to a + 14.	
828239	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 452 of SEQ ID NO:14, b is an integer of 15 to 466, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:14, and where b is greater than or equal to a + 14.	
828242	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 850 of	

	SEQ ID NO:15, b is an integer of 15 to 864, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:15, and where b is greater than or equal to a + 14.	
828247	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2791 of SEQ ID NO:16, b is an integer of 15 to 2805, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:16, and where b is greater than or equal to a + 14.	
828248	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 696 of SEQ ID NO:17, b is an integer of 15 to 710, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:17, and where b is greater than or equal to a + 14.	T66275, R11733, H10020, H10293, AA054067, AA127524, AA192628
828250	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 978 of SEQ ID NO:18, b is an integer of 15 to 992, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:18, and where b is greater than or equal to a + 14.	T52330, T52406, H58954, H59892, H80117, H95961, AA035013, AA233062, AA811863, AA812014, AA827886
828256	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1781 of SEQ ID NO:19, b is an integer of 15 to 1795, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:19, and where b is greater than or equal to a + 14.	R19470, R43810, R43810, R68471, R84396, H48527, H72808, H74042, H77919, N59326, W37177, W63751, AA054952, AA055414, AA075756, AA084216, AA167088, AA171933, AA283637, AA504517, AA526903, AA548976, AA720935, AA743227, AA876493, AA922502, AA935236, AA977747, AA985556, AA995834, AI085874, AI089849, N83890, AA643000
828267	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 695 of SEQ ID NO:20, b is an integer of 15 to 709, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:20, and where b is greater than or equal to a + 14.	R64277, R78171, R81344, R82497, R82551, H30248, N21678, N35076, N43816, N49970, N72024, N72025, W32428, W45005, W47341, W47466, AA023021, AA022495, AA160240, AA161105, AA160827, AA262229, AA460961, AA461270, AA503727, AA516264, AA587486, AA618498, AA577174, AA769656, AA806381, AA804907, AA814296, AA826741, AA872272, AA873216, AA877503, AA887257, AA888574, AA903406, AA946650, AI005204, F18545, AI096504, AI096416,

		C01329
828269	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 635 of SEQ ID NO:21, b is an integer of 15 to 649, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:21, and where b is greater than or equal to a + 14.	
828272	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1593 of SEQ ID NO:22, b is an integer of 15 to 1607, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:22, and where b is greater than or equal to a + 14.	R19809, H18934, H19375, H26539, AA055911, AA494436, AA587324, AA714132, C17882, C18668
828273	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 564 of SEQ ID NO:23, b is an integer of 15 to 578, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:23, and where b is greater than or equal to a + 14.	H19271
828290	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2742 of SEQ ID NO:24, b is an integer of 15 to 2756, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:24, and where b is greater than or equal to a + 14.	T59898, T59989, T94867, T94912, T65240, T65292, T66052, T77599, R09165, R09268, R10580, R10581, T80506, T80507, R16318, R27636, R30800, R35595, R38849, R39241, R41395, R59117, R76584, R76585, H09652, H09692, H11510, H11870, R83218, R91788, R91789, R96324, R96325, H57286, H72668, N74017, W02255, AA148639, AA148693, AA236061, AA236908, AA252747, AA259022, AA262883, AA278784, AA282771, AA284927, AA417594, AA456869, AA457026, AA482034, AA483364, AA483699, AA742268, AA831255
828326	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2666 of SEQ ID NO:25, b is an integer of 15 to 2680, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:25, and where b is greater than or equal to a + 14.	T39632, T51535, T51684, T53316, T53317, T78655, R39299, R50091, R50092, R60242, R60477, H15498, H16190, H16348, H23875, H23876, H39694, H46597, H66845, H66889, H81508, H83033, N71968, N99700, W00835, W42577, W60798, W60929, AA040868, AA043137, AA100392, AA133460, AA133461, AA151301, AA190783, AA190331, AA232148, AA244332, AA244333, AA417836, AA468588, AA552068, AA622100,

		AA570065, AA568384, AA661530, AA689348, AA748424, AA767109, AA769292, AA809791, AA915876, AA931522, AA983494, AI081278, N85117, W22522
828397	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1845 of SEQ ID NO:26, b is an integer of 15 to 1859, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:26, and where b is greater than or equal to a + 14.	
828405	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 620 of SEQ ID NO:27, b is an integer of 15 to 634, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:27, and where b is greater than or equal to a + 14.	N27583
828461	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1618 of SEQ ID NO:28, b is an integer of 15 to 1632, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:28, and where b is greater than or equal to a + 14.	T89996, H96643, AA076642, AA079413, AA120823, AA120824, AA133102, AA128879, AA158349, AA158350, AA838312, C00042, AA642274
828482	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2525 of SEQ ID NO:29, b is an integer of 15 to 2539, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:29, and where b is greater than or equal to a + 14.	R12256, T79977, T81576, T83389, T97268, T97379, R16708, R39343, R69161, R69275, H15410, H15466, H29577, H29661, H50315, N34544, N47100, N62861, N67285, W24823, AA232725, AA236518, AA657840, AA736793, W26725
828488	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 480 of SEQ ID NO:30, b is an integer of 15 to 494, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:30, and where b is greater than or equal to a + 14.	
828491	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the	

	general formula of a-b, where a is any integer between 1 to 1249 of SEQ ID NO:31, b is an integer of 15 to 1263, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:31, and where b is greater than or equal to a + 14.	
828492	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 323 of SEQ ID NO:32, b is an integer of 15 to 337, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:32, and where b is greater than or equal to a + 14.	
828494	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1728 of SEQ ID NO:33, b is an integer of 15 to 1742, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:33, and where b is greater than or equal to a + 14.	T77590, R19349, H06686, N42827, N42891, N73270, W38326, AA180136, AA194183, AA235257, AA424380, AA902702, AA939089, AA977206, AA988001, AA996359
828496	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1152 of SEQ ID NO:34, b is an integer of 15 to 1166, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:34, and where b is greater than or equal to a + 14.	H16641, H81084, AA972362
828498	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1035 of SEQ ID NO:35, b is an integer of 15 to 1049, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:35, and where b is greater than or equal to a + 14.	T39930, T98680, R89124, R89756, R91725, R91820, R92013, R92158, R94233, R94329, H59495, H61480, H62771, H62831, H67085, H67621, H71835, H71836, H79855, H79856, N31924, N42760, N55543, N72715, N76929, N79841, W46350, W46166, H97319, AA730300, AA746151, AA887571, AA918492, AA989417, AI001025, D79228, W38455, C15769
828504	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 475 of SEQ ID NO:36, b is an integer of 15 to 489, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:36, and where b is greater than or equal to a + 14.	
828507	Preferably excluded from the present invention are one or more	

	polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 584 of SEQ ID NO:37, b is an integer of 15 to 598, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:37, and where b is greater than or equal to a + 14.	
828512	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 748 of SEQ ID NO:38, b is an integer of 15 to 762, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:38, and where b is greater than or equal to a + 14.	N27463
828516	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1944 of SEQ ID NO:39, b is an integer of 15 to 1958, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:39, and where b is greater than or equal to a + 14.	T56794, T56795, T84141, R02653, R20890, R24025, R33319, R33320, R34774, R67912, R69738, R77753, R77838, R81629, H15449, H15508, H27402, H58932, H58979, H99151, N20262, N24400, N25962, N29166, N34977, N35438, N50797, N55154, W02966, W92783, W92882, AA007585, AA036747, AA036997, AA074474, AA102125, AA100655, AA112751, AA113219, AA113805, AA188790, AA541250, AA541763, AA558310, AA559035, AA581570, AA587474, AA569332, AA687827, AA715063, AA918342, AA936443, AA937851, AA947124, AA954522, AA989224, AI017059, AI057158, AI088905, AI094996, AI096728, U46434, C01531
828519	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 463 of SEQ ID NO:40, b is an integer of 15 to 477, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:40, and where b is greater than or equal to a + 14.	W79671
828521	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 846 of SEQ ID NO:41, b is an integer of 15 to 860, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:41, and where b is greater than or equal to a + 14.	
828522	Preferably excluded from the present invention are one or more	T54309, T63973, T64041, T89636, T90270, R62731, R63686,

	polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1117 of SEQ ID NO:42, b is an integer of 15 to 1131, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:42, and where b is greater than or equal to a + 14.	H98873, N25098, N36012, N38881, N44246, N67168, AA047726, AA081019, AA120775, AA120774, AA128274, AA128571, AA551864, AA767989, AA902693
828525	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1320 of SEQ ID NO:43, b is an integer of 15 to 1334, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:43, and where b is greater than or equal to a + 14.	T48657, T48687, T48861, T49081, T49118, T53559, T58581, R23090, R26432, R26979, R27855, R32999, R34608, R64482, R64537, R66662, R67745, R69150, R70688, R77130, R81861, R82246, R82815, H03531, N39770, N41593, N42044, N57142, N94149, AA029208, AA149385, AA234086, N26326, N30247, N30819, N32903, N39539, D78905, D79060, N63792, AA029209
828529	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2337 of SEQ ID NO:44, b is an integer of 15 to 2351, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:44, and where b is greater than or equal to a + 14.	
828530	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1573 of SEQ ID NO:45, b is an integer of 15 to 1587, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:45, and where b is greater than or equal to a + 14.	T74290, T79269, R24408, R24409, R32342, R33507, R34284, R70908, H13795, H13794, N42196, AA013089, AA228469, AA505953, AA508121, AA602662, AA631903, AA865676, AA888323, AI032201, AA013090
828536	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 365 of SEQ ID NO:46, b is an integer of 15 to 379, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:46, and where b is greater than or equal to a + 14.	
828537	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1906 of SEQ ID NO:47, b is an integer of 15 to 1920, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:47, and where b is greater than or equal to a + 14.	

828539	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 305 of SEQ ID NO:48, b is an integer of 15 to 319, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:48, and where b is greater than or equal to a + 14.	
828540	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 264 of SEQ ID NO:49, b is an integer of 15 to 278, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:49, and where b is greater than or equal to a + 14.	
828542	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 638 of SEQ ID NO:50, b is an integer of 15 to 652, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:50, and where b is greater than or equal to a + 14.	
828543	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 929 of SEQ ID NO:51, b is an integer of 15 to 943, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:51, and where b is greater than or equal to a + 14.	
828544	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 818 of SEQ ID NO:52, b is an integer of 15 to 832, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:52, and where b is greater than or equal to a + 14.	
828546	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1540 of SEQ ID NO:53, b is an integer of 15 to 1554, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID	H25827, H45313, W77774, AA587295, AA595924, AA603051, C00427

	NO:53, and where b is greater than or equal to a + 14.	
828550	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 267 of SEQ ID NO:54, b is an integer of 15 to 281, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:54, and where b is greater than or equal to a + 14.	
828551	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 793 of SEQ ID NO:55, b is an integer of 15 to 807, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:55, and where b is greater than or equal to a + 14.	AA224996, AA225045, AA229587, AA524970, AA528287, AA569633, AA577923
828553	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 642 of SEQ ID NO:56, b is an integer of 15 to 656, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:56, and where b is greater than or equal to a + 14.	
828557	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 780 of SEQ ID NO:57, b is an integer of 15 to 794, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:57, and where b is greater than or equal to a + 14.	
828560	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1141 of SEQ ID NO:58, b is an integer of 15 to 1155, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:58, and where b is greater than or equal to a + 14.	R77295, R77355, N50880, AA228477, AA229199, AA229332, AA229430, AA229342, AA508222, AA508881, AA508713, AA522664, AA525054, AA531563, AA564505, AA627496, AA569813, AA908306
828561	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 478 of SEQ ID NO:59, b is an integer of 15 to 492, where both a and b	

	correspond to the positions of nucleotide residues shown in SEQ ID NO:59, and where b is greater than or equal to a + 14.	
828565	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1603 of SEQ ID NO:60, b is an integer of 15 to 1617, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:60, and where b is greater than or equal to a + 14.	
828566	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1639 of SEQ ID NO:61, b is an integer of 15 to 1653, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:61, and where b is greater than or equal to a + 14.	T74741, R89314, H66527, H66526, H67472, H67473, H68173, H68172, H96621, H96622, N27775, N28518, N33857, N66931, AA149826, AA151993, AA152072, AA152078, AA188743
828567	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 426 of SEQ ID NO:62, b is an integer of 15 to 440, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:62, and where b is greater than or equal to a + 14.	
828568	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1048 of SEQ ID NO:63, b is an integer of 15 to 1062, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:63, and where b is greater than or equal to a + 14.	R01283, R62995, R63052, R97762, R97763, AA044146, AA044262, AA150771, AA429074, AA282254, AA282728, AA468569, AA586526, AA622172, AA631182, AA631273, AA809910, AA811682
828569	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 408 of SEQ ID NO:64, b is an integer of 15 to 422, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:64, and where b is greater than or equal to a + 14.	
828570	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 695 of	H77440

	SEQ ID NO:65, b is an integer of 15 to 709, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:65, and where b is greater than or equal to a + 14.	
828571	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1288 of SEQ ID NO:66, b is an integer of 15 to 1302, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:66, and where b is greater than or equal to a + 14.	N27429, N34713, N51144, AA033703, AA033704, AA046488, AA046700, AA180131, AA514866, AA515411, AA527426, AA554163, AA745008, AA805885, AA862045, AA953025, AI075070
828574	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1032 of SEQ ID NO:67, b is an integer of 15 to 1046, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:67, and where b is greater than or equal to a + 14.	T92929, T93045, T92007, T92093, T98007, R28667, N79460, AA614258, AA741201, AA847513, AI083735
828575	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 487 of SEQ ID NO:68, b is an integer of 15 to 501, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:68, and where b is greater than or equal to a + 14.	AA837738
828577	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 567 of SEQ ID NO:69, b is an integer of 15 to 581, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:69, and where b is greater than or equal to a + 14.	AA169882, AA169883
828578	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1062 of SEQ ID NO:70, b is an integer of 15 to 1076, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:70, and where b is greater than or equal to a + 14.	T39452, T46945, T47319, T53621, T53622, T61271, T61323, R21194, R22811, R24705, R25199, R50467, R50468, R53758, R53759, R63087, R63131, R63969, R64075, R70570, R77117, R77118, R80611, R80612, H00653, H00742, H02619, H02725, N32242, N57336, N69947, N80785, N98328, N98569, W15554, AA029021, AA029143, AA037587, AA131825, AA131992, AA229266, AA507524, AA533307, AA533431, AA534110, AA534166, AA534281, AA535170, AA586608, AA593596,

		AA838623, AA885780, AA936945, AA642546
828580	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 362 of SEQ ID NO:71, b is an integer of 15 to 376, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:71, and where b is greater than or equal to a + 14.	
828581	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 360 of SEQ ID NO:72, b is an integer of 15 to 374, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:72, and where b is greater than or equal to a + 14.	AA507628
828583	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 405 of SEQ ID NO:73, b is an integer of 15 to 419, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:73, and where b is greater than or equal to a + 14.	
828585	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 272 of SEQ ID NO:74, b is an integer of 15 to 286, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:74, and where b is greater than or equal to a + 14.	AA234220
828587	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 619 of SEQ ID NO:75, b is an integer of 15 to 633, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:75, and where b is greater than or equal to a + 14.	
828590	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 242 of SEQ ID NO:76, b is an integer of 15 to 256, where both a and b	

	correspond to the positions of nucleotide residues shown in SEQ ID NO:76, and where b is greater than or equal to a + 14.	
828592	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 680 of SEQ ID NO:77, b is an integer of 15 to 694, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:77, and where b is greater than or equal to a + 14.	R52221, R54548, R97331, H57211, H55375, H55650
828593	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2548 of SEQ ID NO:78, b is an integer of 15 to 2562, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:78, and where b is greater than or equal to a + 14.	T57629, T58982, R19824, R45052, R45052, R55638, R59495, H18527, H19193, H28411, H39750, H62246, H62335, H91342, N62586, N63264, N80359, W81015, W94481, W94746, AA011589, AA029848, AA028978, AA043902, AA114931, AA114930, AA191597, AA232906, AA233035, AA258137, AA287367, AA287505, AA506450, AA525766, AA526128, AA548114, AA592904, AA808705, AA837733, AA876630, AA908724, N90333, AA007166
828594	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1596 of SEQ ID NO:79, b is an integer of 15 to 1610, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:79, and where b is greater than or equal to a + 14.	R06875, R06876, H89673, AA036961, AA150107, AA150515, AA983641
828596	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1034 of SEQ ID NO:80, b is an integer of 15 to 1048, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:80, and where b is greater than or equal to a + 14.	R09863, T84746, T98848, W01274, W48629, AA082189, AA426550, C04056
828597	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1122 of SEQ ID NO:81, b is an integer of 15 to 1136, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:81, and where b is greater than or equal to a + 14.	R41797, R41797, H61049, N58312, N79783, W07281, W23730, W23738, W35330, W35337, AA235295, AA935231, AA995710, AI017376, AI088874, AI096890, W27549
828598	Preferably excluded from the present invention are one or more	

	polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 283 of SEQ ID NO:82, b is an integer of 15 to 297, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:82, and where b is greater than or equal to a + 14.	
828601	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2136 of SEQ ID NO:83, b is an integer of 15 to 2150, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:83, and where b is greater than or equal to a + 14.	
828605	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 587 of SEQ ID NO:84, b is an integer of 15 to 601, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:84, and where b is greater than or equal to a + 14.	
828608	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 520 of SEQ ID NO:85, b is an integer of 15 to 534, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:85, and where b is greater than or equal to a + 14.	AA244003, AA244034, AA506324
828609	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1023 of SEQ ID NO:86, b is an integer of 15 to 1037, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:86, and where b is greater than or equal to a + 14.	N48056, N52932, N53254, N64840, N75691, AI050871
828610	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 583 of SEQ ID NO:87, b is an integer of 15 to 597, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:87, and where b is greater than or equal to a + 14.	AA177029, AA177023, AA176984, AA177153, AA216404, AA224959, AA225025, AA225109, AA225143, AA225206, AA225152, AA225228, AA225308, AA225322, AA225213, AA225409, AA225879, AA225880, AA225963, AA225974, AA226101, AA226227, AA226240, AA226384, AA226459, AA226556, AA226623, AA226632, AA226680, AA229222,

		AA229223, AA229482, AA229756, AA229964, AA244017, AA244091, AA244178, AA244052, AA244362, AA244452, AA397457, AA420631, AA420632, AA420633, AA420826, AA469131, AA469154, AA469201, AA469209, AA469226, AA469293, AA469373, AA470501, AA470548, AA492204, AA492255, AA492295, AA492311, AA492312, AA492327, AA492329, AA492334, AA492382, AA492389, AA492411, AA492438, AA492445, AA492451, AA494242, AA494243, AA494246, AA493268, AA493332, AA493445, AA502071, AA502154, AA502180, AA502191, AA502200, AA502978, AA502981, AA503115, AA503349, AA503429, AA503609, AA503666, AA503677, AA503682, AA503909, AA503926, AA504051, AA504066, AA506197, AA506319, AA506330, AA506475, AA506731, AA506804, AA506914, AA507128, AA507215, AA507217, AA507281, AA507287, AA507305, AA507373, AA507510, AA507545, AA507615, AA507633, AA507659, AA507664, AA507669, AA507679, AA507685, AA507759, AA507769, AA507778, AA507785, AA507789, AA507968, AA507983, AA507996, AA507995, AA508013, AA508078, AA508096, AA508112, AA508128, AA508144, AA508348, AA508360, AA508636, AA513240, AA514804, AA514915, AA516492, AA516500, AA522599, AA524675, AA524914, AA524998, AA525091, AA526491, AA526493, AA527728, AA527825, AA528273, AA530882, AA530906, AA530942, AA530954, AA531208, AA531341, AA531361, AA531381, AA531498, AA532578, AA532712, AA532960, AA533031, AA533053, AA533162, AA533961, AA534135, AA535497, AA535744, AA541576, AA541642, AA548220, AA548400, AA551463, AA551698, AA551727, AA551737, AA552827, AA552829, AA557784, AA557804, AA558634, AA564543, AA564966, AA565164, AA588853, AA588270, AA587824, AA588630, AA593049, AA593065, AA594830, AA594923, AA595627, AA603351, AA603362, AA603437, AA603827, AA603877, AA603879, AA630927, AA635332, AA635394, AA635542, AA635549, AA635909, AA636004, AA639312, AA639995, AA640184, AA640298, AA640342,

		AA569556, AA570614, AA572857, AA574208, AA574209, AA574212, AA574273, AA580026, AA578701, AA578799, AA578900, AA579004, AA579008, AA579351, AA568108, AA568415, AA654920, AA654956, AA657393, AA657432, AA657479, AA657506, AA657531, AA657541, AA657686, AA657800, AA657938, AA658414, AA658873, AA659224, AA659592, AA659778, AA661727, AA662090, AA662125, AA662301, AA687536, AA687632, AA715325, AA807843, AA809523, AA809593, AA640904, AA640929, AA642080, AA642520
828617	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 460 of SEQ ID NO:88, b is an integer of 15 to 474, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:88, and where b is greater than or equal to a + 14.	
828620	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1523 of SEQ ID NO:89, b is an integer of 15 to 1537, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:89, and where b is greater than or equal to a + 14.	AA228288, AA492280, AA507777, AA508355, AA527737, AA527805, AA559165, AA559352, AA564484, AA602957, AA659719, AA642055
828621	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 290 of SEQ ID NO:90, b is an integer of 15 to 304, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:90, and where b is greater than or equal to a + 14.	
828622	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 355 of SEQ ID NO:91, b is an integer of 15 to 369, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:91, and where b is greater than or equal to a + 14.	AA570443
828623	Preferably excluded from the present invention are one or more	

	polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 301 of SEQ ID NO:92, b is an integer of 15 to 315, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:92, and where b is greater than or equal to a + 14.	
828625	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 687 of SEQ ID NO:93, b is an integer of 15 to 701, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:93, and where b is greater than or equal to a + 14.	
828632	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 445 of SEQ ID NO:94, b is an integer of 15 to 459, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:94, and where b is greater than or equal to a + 14.	
828635	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2575 of SEQ ID NO:95, b is an integer of 15 to 2589, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:95, and where b is greater than or equal to a + 14.	R13230, R19016, R35012, R40312, R44087, R46776, R49399, R44087, R40312, R49399, H22883, H24275, H71951, N73720, W03891, W95360, W95359, AA055316, AA055317, AA135153, AA135291, AA195210, AA195427, AA236624, AA237000, AA548249, AA553712, AA595319, AA770603, AA947028, D78699
828637	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 443 of SEQ ID NO:96, b is an integer of 15 to 457, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:96, and where b is greater than or equal to a + 14.	
828639	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 502 of SEQ ID NO:97, b is an integer of 15 to 516, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:97, and where b is greater than or equal to a + 14.	

828645	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 300 of SEQ ID NO:98, b is an integer of 15 to 314, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:98, and where b is greater than or equal to a + 14.	
828648	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 665 of SEQ ID NO:99, b is an integer of 15 to 679, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:99, and where b is greater than or equal to a + 14.	
828649	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 585 of SEQ ID NO:100, b is an integer of 15 to 599, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:100, and where b is greater than or equal to a + 14.	
828651	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1175 of SEQ ID NO:101, b is an integer of 15 to 1189, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:101, and where b is greater than or equal to a + 14.	
828652	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 237 of SEQ ID NO:102, b is an integer of 15 to 251, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:102, and where b is greater than or equal to a + 14.	
828655	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 444 of SEQ ID NO:103, b is an integer of 15 to 458, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID	

	NO:103, and where b is greater than or equal to a + 14.	
828657	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 425 of SEQ ID NO:104, b is an integer of 15 to 439, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:104, and where b is greater than or equal to a + 14.	
828660	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 219 of SEQ ID NO:105, b is an integer of 15 to 233, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:105, and where b is greater than or equal to a + 14.	
828663	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 690 of SEQ ID NO:106, b is an integer of 15 to 704, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:106, and where b is greater than or equal to a + 14.	
828666	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 431 of SEQ ID NO:107, b is an integer of 15 to 445, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:107, and where b is greater than or equal to a + 14.	
828668	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 578 of SEQ ID NO:108, b is an integer of 15 to 592, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:108, and where b is greater than or equal to a + 14.	
828669	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 367 of SEQ ID NO:109, b is an integer of 15 to 381, where both a and b	

	correspond to the positions of nucleotide residues shown in SEQ ID NO:109, and where b is greater than or equal to a + 14.	
828670	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 337 of SEQ ID NO:110, b is an integer of 15 to 351, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:110, and where b is greater than or equal to a + 14.	W38772
828671	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1569 of SEQ ID NO:111, b is an integer of 15 to 1583, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:111, and where b is greater than or equal to a + 14.	
828672	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 417 of SEQ ID NO:112, b is an integer of 15 to 431, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:112, and where b is greater than or equal to a + 14.	
828675	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2828 of SEQ ID NO:113, b is an integer of 15 to 2842, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:113, and where b is greater than or equal to a + 14.	T56042, T56076, T39529, T39565, R20801, R20914, R99174, W76346, AA070283, AA100602, AA186719, AA192887, AA258594, AA258623, AA262429, AA458551, AA425795, AA426147, AA426000, AA428422, AA428672, AA429274, AA429569, AA429700, AA280808, AA280860, AA583152, AA604621, AA573460, AA737552, AA745643, AA809317, AA811436, AA831842, AA832058, AA837490, AA847879, AI089925, AA070162
828677	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 254 of SEQ ID NO:114, b is an integer of 15 to 268, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:114, and where b is greater than or equal to a + 14.	
828678	Preferably excluded from the present invention are one or more	

	polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 786 of SEQ ID NO:115, b is an integer of 15 to 800, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:115, and where b is greater than or equal to a + 14.	
828679	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 632 of SEQ ID NO:116, b is an integer of 15 to 646, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:116, and where b is greater than or equal to a + 14.	
828680	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1520 of SEQ ID NO:117, b is an integer of 15 to 1534, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:117, and where b is greater than or equal to a + 14.	N64514, N70990, W01522, AA025937, AA025996, AA210760, AA215724, AA761682, AA768989, AA911839
828681	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 325 of SEQ ID NO:118, b is an integer of 15 to 339, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:118, and where b is greater than or equal to a + 14.	
828682	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 651 of SEQ ID NO:119, b is an integer of 15 to 665, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:119, and where b is greater than or equal to a + 14.	
828683	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 608 of SEQ ID NO:120, b is an integer of 15 to 622, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:120, and where b is greater than or equal to a + 14.	

828686	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 875 of SEQ ID NO:121, b is an integer of 15 to 889, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:121, and where b is greater than or equal to a + 14.	
828687	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 118 of SEQ ID NO:122, b is an integer of 15 to 132, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:122, and where b is greater than or equal to a + 14.	
828688	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1886 of SEQ ID NO:123, b is an integer of 15 to 1900, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:123, and where b is greater than or equal to a + 14.	T92794, T92816, N50876, W20089, N90429, AA086404, AA112766, AA130846, AA195042, AA194974, AA235868, AA554284, AA639411, AA573456, AA804901, AA828540
828689	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1236 of SEQ ID NO:124, b is an integer of 15 to 1250, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:124, and where b is greater than or equal to a + 14.	
828692	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1175 of SEQ ID NO:125, b is an integer of 15 to 1189, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:125, and where b is greater than or equal to a + 14.	T72780, R07981, R09868, T96304, H51978
828693	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 414 of SEQ ID NO:126, b is an integer of 15 to 428, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID	

	NO:126, and where b is greater than or equal to a + 14.	
828694	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 631 of SEQ ID NO:127, b is an integer of 15 to 645, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:127, and where b is greater than or equal to a + 14.	R02262
828696	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 482 of SEQ ID NO:128, b is an integer of 15 to 496, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:128, and where b is greater than or equal to a + 14.	
828697	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 410 of SEQ ID NO:129, b is an integer of 15 to 424, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:129, and where b is greater than or equal to a + 14.	AA059063
828699	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1695 of SEQ ID NO:130, b is an integer of 15 to 1709, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:130, and where b is greater than or equal to a + 14.	R75912, H40206, H40207, H41559, R87478, H52696, H52717, N40190, AA503759, AA504325, AA553825, AA553899, H64647, AA582193, AA580220, AA687790, AA809845, AA917674, AA935183, AI004172, AI027576, C14410, C14461, C14497, C14511
828702	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 852 of SEQ ID NO:131, b is an integer of 15 to 866, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:131, and where b is greater than or equal to a + 14.	N79392
828703	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1579 of SEQ ID NO:132, b is an integer of 15 to 1593, where both a and b	T69829, R59224, H11661, AA587352, AA807572, AA806747, AA865576, AA912231, AI002338

	correspond to the positions of nucleotide residues shown in SEQ ID NO:132, and where b is greater than or equal to a + 14.	
828704	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 394 of SEQ ID NO:133, b is an integer of 15 to 408, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:133, and where b is greater than or equal to a + 14.	
828706	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2727 of SEQ ID NO:134, b is an integer of 15 to 2741, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:134, and where b is greater than or equal to a + 14.	AA099313, AA099927, AA101522, AA101521, AA102781, AA102782, AA126249, AA134732, AA459009, AA459230, AA524248, AA524247, AA622869, AA744977, AA933725, AI000417, U65740
828708	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 672 of SEQ ID NO:135, b is an integer of 15 to 686, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:135, and where b is greater than or equal to a + 14.	AA736960
828711	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 228 of SEQ ID NO:136, b is an integer of 15 to 242, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:136, and where b is greater than or equal to a + 14.	
828712	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 531 of SEQ ID NO:137, b is an integer of 15 to 545, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:137, and where b is greater than or equal to a + 14.	
828713	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 382 of	

	SEQ ID NO:138, b is an integer of 15 to 396, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:138, and where b is greater than or equal to a + 14.	
828714	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2757 of SEQ ID NO:139, b is an integer of 15 to 2771, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:139, and where b is greater than or equal to a + 14.	
828715	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 408 of SEQ ID NO:140, b is an integer of 15 to 422, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:140, and where b is greater than or equal to a + 14.	
828718	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1616 of SEQ ID NO:141, b is an integer of 15 to 1630, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:141, and where b is greater than or equal to a + 14.	R52059, R52058, H85868, W92475, AA046292, AA463500, AA463546, AA576113, AA862446
828723	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 250 of SEQ ID NO:142, b is an integer of 15 to 264, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:142, and where b is greater than or equal to a + 14.	
828726	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 622 of SEQ ID NO:143, b is an integer of 15 to 636, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:143, and where b is greater than or equal to a + 14.	
828728	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the	N39508, W05658, AA083301, AA159253, AA195825

	general formula of a-b, where a is any integer between 1 to 486 of SEQ ID NO:144, b is an integer of 15 to 500, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:144, and where b is greater than or equal to a + 14.	
828730	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1931 of SEQ ID NO:145, b is an integer of 15 to 1945, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:145, and where b is greater than or equal to a + 14.	
828732	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1100 of SEQ ID NO:146, b is an integer of 15 to 1114, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:146, and where b is greater than or equal to a + 14.	
828733	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 532 of SEQ ID NO:147, b is an integer of 15 to 546, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:147, and where b is greater than or equal to a + 14.	
828735	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1749 of SEQ ID NO:148, b is an integer of 15 to 1763, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:148, and where b is greater than or equal to a + 14.	
828736	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 357 of SEQ ID NO:149, b is an integer of 15 to 371, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:149, and where b is greater than or equal to a + 14.	
828739	Preferably excluded from the present invention are one or more	R36043

	polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 418 of SEQ ID NO:150, b is an integer of 15 to 432, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:150, and where b is greater than or equal to a + 14.	
828740	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 387 of SEQ ID NO:151, b is an integer of 15 to 401, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:151, and where b is greater than or equal to a + 14.	
828742	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 837 of SEQ ID NO:152, b is an integer of 15 to 851, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:152, and where b is greater than or equal to a + 14.	
828748	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1664 of SEQ ID NO:153, b is an integer of 15 to 1678, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:153, and where b is greater than or equal to a + 14.	AA225966, AA226113, AA229173, AA229167, AA229535, AA243985, AA244099, AA244206, AA259243, AA420690, AA467761, AA467944, AA468120, AA468151, AA468187, AA468326, AA468918, AA468995, AA469129, AA469199, AA470575, AA502955, AA503272, AA506649, AA507335, AA507799, AA514825, AA522473, AA522848, AA524651, AA524893, AA525058, AA531386, AA532387, AA532926, AA534072, AA534246, AA535303, AA535837, AA551447, AA551738, AA558900, AA588263, AA587715, AA593380, AA595047, AA595357, AA595465, AA595601, AA603572, AA604709, AA635888, AA640473, AA569666, AA569670, AA573539, AA573587, AA574390, AA578439, AA578628, AA579001, AA579026, AA579117, AA579310, AA565962, AA566046, AA654974, AA657781, AA657831, AA658156, AA658207, AA658243, AA658463, AA658877, AA659198, AA659306, AA687563, AA687852, AA742871, AA876666, AA887095, AA888488, AA934855, AA935419, AA937807, AA937854, AA978237

828749	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1144 of SEQ ID NO:154, b is an integer of 15 to 1158, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:154, and where b is greater than or equal to a + 14.	T65384, R46577, R52660, R46577, H11492, N73810, N99718, AA121044, AA126520, AA126579, AA126687
828752	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1955 of SEQ ID NO:155, b is an integer of 15 to 1969, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:155, and where b is greater than or equal to a + 14.	AA492170
828753	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 386 of SEQ ID NO:156, b is an integer of 15 to 400, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:156, and where b is greater than or equal to a + 14.	
828754	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 708 of SEQ ID NO:157, b is an integer of 15 to 722, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:157, and where b is greater than or equal to a + 14.	N42714, N32500
828757	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1186 of SEQ ID NO:158, b is an integer of 15 to 1200, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:158, and where b is greater than or equal to a + 14.	T90246, T90691, R14702, R34647, R42424, R49176, R42424, R49176, H06287, H06339, H14778, N69116, C03936, C15913
828761	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 331 of SEQ ID NO:159, b is an integer of 15 to 345, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID	

	NO:159, and where b is greater than or equal to a + 14.	
828762	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 462 of SEQ ID NO:160, b is an integer of 15 to 476, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:160, and where b is greater than or equal to a + 14.	
828764	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 506 of SEQ ID NO:161, b is an integer of 15 to 520, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:161, and where b is greater than or equal to a + 14.	
828765	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 325 of SEQ ID NO:162, b is an integer of 15 to 339, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:162, and where b is greater than or equal to a + 14.	
828766	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 343 of SEQ ID NO:163, b is an integer of 15 to 357, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:163, and where b is greater than or equal to a + 14.	
828767	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1065 of SEQ ID NO:164, b is an integer of 15 to 1079, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:164, and where b is greater than or equal to a + 14.	
828768	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1311 of SEQ ID NO:165, b is an integer of 15 to 1325, where both a and b	

	correspond to the positions of nucleotide residues shown in SEQ ID NO:165, and where b is greater than or equal to a + 14.	
828770	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 380 of SEQ ID NO:166, b is an integer of 15 to 394, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:166, and where b is greater than or equal to a + 14.	
828771	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 503 of SEQ ID NO:167, b is an integer of 15 to 517, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:167, and where b is greater than or equal to a + 14.	
828772	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 327 of SEQ ID NO:168, b is an integer of 15 to 341, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:168, and where b is greater than or equal to a + 14.	
828773	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 336 of SEQ ID NO:169, b is an integer of 15 to 350, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:169, and where b is greater than or equal to a + 14.	
828775	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 427 of SEQ ID NO:170, b is an integer of 15 to 441, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:170, and where b is greater than or equal to a + 14.	
828776	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 389 of	AA127485

	SEQ ID NO:171, b is an integer of 15 to 403, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:171, and where b is greater than or equal to a + 14.	
828777	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 970 of SEQ ID NO:172, b is an integer of 15 to 984, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:172, and where b is greater than or equal to a + 14.	T86451, R87531, R87627, R91402, R92659, H98729, N24299, W19089, W20421, AA454940, AA605076, AA639539, AA662751, AA714010, AA743934, AA746310, AA888099, AA953728, AA976688, AI027564
828778	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1180 of SEQ ID NO:173, b is an integer of 15 to 1194, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:173, and where b is greater than or equal to a + 14.	
828780	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 687 of SEQ ID NO:174, b is an integer of 15 to 701, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:174, and where b is greater than or equal to a + 14.	
828781	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1167 of SEQ ID NO:175, b is an integer of 15 to 1181, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:175, and where b is greater than or equal to a + 14.	R17769, R39304, R42342, R42342, R61526, H05114, H08622, N63035, AA039717, AA039716, AA039852, AA235700, AA255466, AA461108, AA918115, AA938595, W00511, C00278
828782	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 475 of SEQ ID NO:176, b is an integer of 15 to 489, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:176, and where b is greater than or equal to a + 14.	
828783	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the	

	general formula of a-b, where a is any integer between 1 to 239 of SEQ ID NO:177, b is an integer of 15 to 253, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:177, and where b is greater than or equal to a + 14.	
828784	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 379 of SEQ ID NO:178, b is an integer of 15 to 393, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:178, and where b is greater than or equal to a + 14.	
828785	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 451 of SEQ ID NO:179, b is an integer of 15 to 465, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:179, and where b is greater than or equal to a + 14.	H28735, AA541256, AA935694
828786	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 518 of SEQ ID NO:180, b is an integer of 15 to 532, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:180, and where b is greater than or equal to a + 14.	T50920
828788	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 800 of SEQ ID NO:181, b is an integer of 15 to 814, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:181, and where b is greater than or equal to a + 14.	AA765439
828790	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 303 of SEQ ID NO:182, b is an integer of 15 to 317, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:182, and where b is greater than or equal to a + 14.	
828791	Preferably excluded from the present invention are one or more	

	polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 229 of SEQ ID NO:183, b is an integer of 15 to 243, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:183, and where b is greater than or equal to a + 14.	
828792	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1134 of SEQ ID NO:184, b is an integer of 15 to 1148, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:184, and where b is greater than or equal to a + 14.	
828794	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1957 of SEQ ID NO:185, b is an integer of 15 to 1971, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:185, and where b is greater than or equal to a + 14.	
828797	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 352 of SEQ ID NO:186, b is an integer of 15 to 366, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:186, and where b is greater than or equal to a + 14.	
828798	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 336 of SEQ ID NO:187, b is an integer of 15 to 350, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:187, and where b is greater than or equal to a + 14.	
828799	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 361 of SEQ ID NO:188, b is an integer of 15 to 375, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:188, and where b is greater than or equal to a + 14.	R92181

828801	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 351 of SEQ ID NO:189, b is an integer of 15 to 365, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:189, and where b is greater than or equal to a + 14.	
828802	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 803 of SEQ ID NO:190, b is an integer of 15 to 817, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:190, and where b is greater than or equal to a + 14.	
828803	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 576 of SEQ ID NO:191, b is an integer of 15 to 590, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:191, and where b is greater than or equal to a + 14.	
828804	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 294 of SEQ ID NO:192, b is an integer of 15 to 308, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:192, and where b is greater than or equal to a + 14.	
828805	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 329 of SEQ ID NO:193, b is an integer of 15 to 343, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:193, and where b is greater than or equal to a + 14.	
828807	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 676 of SEQ ID NO:194, b is an integer of 15 to 690, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID	AA507550, AA613671, AA991871, AI073898

	NO:194, and where b is greater than or equal to a + 14.	
828809	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 223 of SEQ ID NO:195, b is an integer of 15 to 237, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:195, and where b is greater than or equal to a + 14.	
828810	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 253 of SEQ ID NO:196, b is an integer of 15 to 267, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:196, and where b is greater than or equal to a + 14.	
828811	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 429 of SEQ ID NO:197, b is an integer of 15 to 443, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:197, and where b is greater than or equal to a + 14.	
828817	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 194 of SEQ ID NO:198, b is an integer of 15 to 208, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:198, and where b is greater than or equal to a + 14.	
828818	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 244 of SEQ ID NO:199, b is an integer of 15 to 258, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:199, and where b is greater than or equal to a + 14.	
828819	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 879 of SEQ ID NO:200, b is an integer of 15 to 893, where both a and b	R28397, R35050, R82429, AA523252, AA541515, AA888589, AA931260, AA969512, N90287

	correspond to the positions of nucleotide residues shown in SEQ ID NO:200, and where b is greater than or equal to a + 14.	
828820	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 489 of SEQ ID NO:201, b is an integer of 15 to 503, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:201, and where b is greater than or equal to a + 14.	
828821	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 424 of SEQ ID NO:202, b is an integer of 15 to 438, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:202, and where b is greater than or equal to a + 14.	
828823	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 862 of SEQ ID NO:203, b is an integer of 15 to 876, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:203, and where b is greater than or equal to a + 14.	
828824	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1490 of SEQ ID NO:204, b is an integer of 15 to 1504, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:204, and where b is greater than or equal to a + 14.	T63961, R37805, R41200, R41200, H06703, H14569, N35284, W84891, W84386, AA020009, AA115923, AA191098, AA720881, AA825322, AA007194
828825	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 511 of SEQ ID NO:205, b is an integer of 15 to 525, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:205, and where b is greater than or equal to a + 14.	T90840, R97506, R97507, H56561, H90159, AA548594
828826	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2480 of	R54121, H53524, H83780, N33845, AA150188, AA150364, AA193510, AA236206, AA236207, AA256878, AA255472, AA292484, AA292485, AA514616, AA808712, AA812205

	SEQ ID NO:206, b is an integer of 15 to 2494, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:206, and where b is greater than or equal to a + 14.	
828829	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 866 of SEQ ID NO:207, b is an integer of 15 to 880, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:207, and where b is greater than or equal to a + 14.	
828830	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 626 of SEQ ID NO:208, b is an integer of 15 to 640, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:208, and where b is greater than or equal to a + 14.	W47311
828833	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 289 of SEQ ID NO:209, b is an integer of 15 to 303, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:209, and where b is greater than or equal to a + 14.	
828835	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1154 of SEQ ID NO:210, b is an integer of 15 to 1168, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:210, and where b is greater than or equal to a + 14.	
828838	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3119 of SEQ ID NO:211, b is an integer of 15 to 3133, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:211, and where b is greater than or equal to a + 14.	
828840	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the	T67663, N51807, N94795

	general formula of a-b, where a is any integer between 1 to 666 of SEQ ID NO:212, b is an integer of 15 to 680, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:212, and where b is greater than or equal to a + 14.	
828845	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 549 of SEQ ID NO:213, b is an integer of 15 to 563, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:213, and where b is greater than or equal to a + 14.	AA278542
828846	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2622 of SEQ ID NO:214, b is an integer of 15 to 2636, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:214, and where b is greater than or equal to a + 14.	
828847	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1808 of SEQ ID NO:215, b is an integer of 15 to 1822, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:215, and where b is greater than or equal to a + 14.	
828849	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3113 of SEQ ID NO:216, b is an integer of 15 to 3127, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:216, and where b is greater than or equal to a + 14.	
828850	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1515 of SEQ ID NO:217, b is an integer of 15 to 1529, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:217, and where b is greater than or equal to a + 14.	T89442, T89529, R00855, R01510, R17037, R44677, R44677, W71999, W76568, AA028176, AA594435, AA630811, AA640365, AA570503, AA827402, AI001038
828852	Preferably excluded from the present invention are one or more	N25191, N51394, AA085653

	polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1086 of SEQ ID NO:218, b is an integer of 15 to 1100, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:218, and where b is greater than or equal to a + 14.	
828853	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1778 of SEQ ID NO:219, b is an integer of 15 to 1792, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:219, and where b is greater than or equal to a + 14.	T69893, R23246, R23322, R23610, R26164, R76851, R78355, R78356, W37071, AA281297, AA281298, AA287617, AA286726, AA830753, AA907191, AA937081
828857	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1296 of SEQ ID NO:220, b is an integer of 15 to 1310, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:220, and where b is greater than or equal to a + 14.	H87149, N29514, N32038, W49771, W69834, W69944, W69906, W70171, AA035645, AA262486, AA280793, AA280787, AA468735, AA470769, AA814845, AA877855, AA903806
828861	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1355 of SEQ ID NO:221, b is an integer of 15 to 1369, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:221, and where b is greater than or equal to a + 14.	
828866	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 778 of SEQ ID NO:222, b is an integer of 15 to 792, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:222, and where b is greater than or equal to a + 14.	R17863, H06471, AA157721
828872	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 907 of SEQ ID NO:223, b is an integer of 15 to 921, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:223, and where b is greater than or equal to a + 14.	R87888, R87900, R87908, N49168, AA931266

828874	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1965 of SEQ ID NO:224, b is an integer of 15 to 1979, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:224, and where b is greater than or equal to a + 14.	T87038, R70347, H39025, R91475, H57830, H59954, H62220, H62316, H65258, H65259, H95743, N54406, W25201, W32973, W69360, W69399, W84707, W90181, AA045489, AA058908, AA059484, AA126289, AA126390, AA127568, AA171412, AA171832, AA548030, AA593288, AA595330, AA622098, AA573531, AA574415, AA865443
828875	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 527 of SEQ ID NO:225, b is an integer of 15 to 541, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:225, and where b is greater than or equal to a + 14.	
828877	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 263 of SEQ ID NO:226, b is an integer of 15 to 277, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:226, and where b is greater than or equal to a + 14.	
828878	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2055 of SEQ ID NO:227, b is an integer of 15 to 2069, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:227, and where b is greater than or equal to a + 14.	T66330, R26894, R27126, R69123, R69242, R82299, R82300, W07548, W40127, W61081, W63740, AA088736, AA088851, AA416637, AA425692, AA587736, AA574419, AA659481, AA746137, AA827964, AA873416, AA876962, AA886118, AA913307, W63541, AA091722
828879	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 457 of SEQ ID NO:228, b is an integer of 15 to 471, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:228, and where b is greater than or equal to a + 14.	
828881	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1626 of SEQ ID NO:229, b is an integer of 15 to 1640, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID	

	NO:229, and where b is greater than or equal to a + 14.	
828885	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1956 of SEQ ID NO:230, b is an integer of 15 to 1970, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:230, and where b is greater than or equal to a + 14.	T66265, R00322, R05577, R14288, R40578, N35835, W67698, W68707, AA226782, AA227401, AA917573, AI096970, C01407
828886	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 296 of SEQ ID NO:231, b is an integer of 15 to 310, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:231, and where b is greater than or equal to a + 14.	
828887	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2819 of SEQ ID NO:232, b is an integer of 15 to 2833, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:232, and where b is greater than or equal to a + 14.	
828889	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 678 of SEQ ID NO:233, b is an integer of 15 to 692, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:233, and where b is greater than or equal to a + 14.	AI084904, N87764
828891	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1339 of SEQ ID NO:234, b is an integer of 15 to 1353, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:234, and where b is greater than or equal to a + 14.	
828899	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 332 of SEQ ID NO:235, b is an integer of 15 to 346, where both a and b	

	correspond to the positions of nucleotide residues shown in SEQ ID NO:235, and where b is greater than or equal to a + 14.	
828907	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2257 of SEQ ID NO:236, b is an integer of 15 to 2271, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:236, and where b is greater than or equal to a + 14.	
828911	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3036 of SEQ ID NO:237, b is an integer of 15 to 3050, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:237, and where b is greater than or equal to a + 14.	
828914	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2788 of SEQ ID NO:238, b is an integer of 15 to 2802, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:238, and where b is greater than or equal to a + 14.	
828917	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1523 of SEQ ID NO:239, b is an integer of 15 to 1537, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:239, and where b is greater than or equal to a + 14.	T48789, T48790, T52689, T52690, T54143, T57627, T58981, T60334, T63023, T63169, T64611, T68165, T73770, T92858, R09683, R05784, R05870, R23705, R24243, R25436, R26263, R26661, R31482, R33617, R52663, R54888, R55790, R63634, R64491, R65588, R66756, R74348, R74447, R77767, R77861, H24648, H24647, H25483, H25708, H25719, H30170, H39683, H42201, H50627, H61272, H74187, H73366, H84457, H96852, H97161, N21258, N24067, N25124, N25891, N32256, N35943, N39665, N59887, N74237, N75946, N77028, N91815, N94382, W01241, W04970, W16791, W31249, W37991, W42625, W42503, W42504, W45097, W46997, W47010, W47011, W47035, W58226, W60191, W74239, AA011342, AA011422, AA053421, AA053142, AA069730, AA069687, AA071401, AA079362, AA085841, AA088476, AA088867, AA099339, AA098900, AA099401, AA099509, AA099626, AA100481,

		AA111899, AA112344, AA128689, AA128504, AA130068, AA130069, AA133988, AA130205, AA134388, AA130699, AA131164, AA131119, AA135908, AA143614, AA148147, AA151655, AA151855, AA149710, AA150148, AA152217, AA150454, AA156656, AA156942, AA158064, AA158065, AA160927, AA167640, AA167760, AA173558, AA173723, AA188571, AA188806, AA188862, AA190996, AA191121, AA252461, AA286842, AA513431, AA523544, AA533369, AA534903, AA541751, AA548088, AA552311, AA563748, AA563790, AA564990, AA565005, AA588690, AA594295, AA600956, AA604061, AA604282, AA604810, AA614124, AA631612, AA632221, AA569331, AA573854, AA577627, AA579851, AA661566, AA689517, AA740358, AA740572, AA747358, AA768322, AA827032, AA831321, AA831490, AA862010, AA862071, AA872486, AA876655, AA878041, AA902900, AA907481, AA932203, AA976947, AA995848, AI005047, AI051152, AI053717, AI053913, AI053985, AI054236, F18795, D82560, W28635, W68223, C02865, C05961, C06214, C14019, AA641827, AA642221
828921	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1320 of SEQ ID NO:240, b is an integer of 15 to 1334, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:240, and where b is greater than or equal to a + 14.	
828922	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2424 of SEQ ID NO:241, b is an integer of 15 to 2438, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:241, and where b is greater than or equal to a + 14.	R14071, R40196, R40196, W78082, AA002041, AA001835, AA167058, AA564814, AA604562, AA831678, AA902298, AA922990, N88270
828924	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 125 of SEQ ID NO:242, b is an integer of 15 to 139, where both a and b	

	correspond to the positions of nucleotide residues shown in SEQ ID NO:242, and where b is greater than or equal to a + 14.	
828925	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 465 of SEQ ID NO:243, b is an integer of 15 to 479, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:243, and where b is greater than or equal to a + 14.	
828926	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 570 of SEQ ID NO:244, b is an integer of 15 to 584, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:244, and where b is greater than or equal to a + 14.	AA021328, AA165340
828928	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 318 of SEQ ID NO:245, b is an integer of 15 to 332, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:245, and where b is greater than or equal to a + 14.	
828930	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1603 of SEQ ID NO:246, b is an integer of 15 to 1617, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:246, and where b is greater than or equal to a + 14.	R13197, R22953, R23059, R34735, H16860, H17441, H30722, H96486, H98091, N25031, N26040, W37582, W74506, W73933, W79218, W79053, AA017108, AA027970, AA027971, AA058997, AA223857, AA468648, AA506695, AA513402, AA627542, AA627543, AA687974, AA748356, AA749265, AA766155, AA769265, AA810698, AA810803, AA811177, AA813864, AA815128, AA837374, AA907206, AA907432, AA911140, AA911319, AA989380, AI088862, N85247
828935	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1435 of SEQ ID NO:247, b is an integer of 15 to 1449, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:247, and where b is greater than or equal to a + 14.	
828937	Preferably excluded from the present invention are one or more	T78834, T78835, T99250, T99297, R12511, T26404, R37406,

	polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1470 of SEQ ID NO:248, b is an integer of 15 to 1484, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:248, and where b is greater than or equal to a + 14.	R41280, R41370, R41371, R52358, R52359, R41280, R41370, R41371, R81208, R81320, R82778, H44863, H54693, H54584, H71670, H72234, H79199, H80064, H80065, H90038, H90715, H96868, H96874, H98754, N20017, N21625, N23354, N28826, N28864, N31950, N33092, N35337, N35930, N36772, N44708, N59759, N63774, N64419, N70550, N73583, N75550, N78219, N78798, N92686, N93067, W06846, W07226, W32114, W32172, W35376, W38996, W39688, W45043, W55883, W55882, W58545, W58627, W68228, W78990, W80596, W87464, N91505, AA026436, AA062585, AA112289, AA127552, AA127553, AA171942, AA172148, AA224492, AA279390, AA505278, AA505337, AA527368, AA531405, AA532853, AA534544, AA535699, AA582848, AA587609, AA568827, AA635925, AA576357, AA576891, AA579716, AA565856, AA687556, AA736748, AA877644, AA885760, AA917890, AA918826, AA938647, AA953594, AA971036, AA973846, AA976240, AA976836, AA948139, AI086410, W01797, N86155, N86407, AA026382, AA092135, AA093922, AA094184
828940	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2408 of SEQ ID NO:249, b is an integer of 15 to 2422, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:249, and where b is greater than or equal to a + 14.	T61139, H60808, H66215, H86154, H86598, N66951, AA045564, AA053520, AA054053, AA054010, AA055556, AA055592, AA055887, AA085899, AA088546, AA100472, AA102305, AA100774, AA115726, AA115790, AA130430, AA130456, AA134504, AA130756, AA132265, AA134988, AA135921, AA143560, AA143592, AA146693, AA146644, AA146790, AA152341, AA149726, AA149780, AA152003, AA157705, AA157715, AA157718, AA157719, AA157730, AA180379, AA226737, AA227302, AA527374, C05254
828942	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 560 of SEQ ID NO:250, b is an integer of 15 to 574, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:250, and where b is greater than or equal to a + 14.	H51878
828943	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the	

	general formula of a-b, where a is any integer between 1 to 1030 of SEQ ID NO:251, b is an integer of 15 to 1044, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:251, and where b is greater than or equal to a + 14.	
828946	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1015 of SEQ ID NO:252, b is an integer of 15 to 1029, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:252, and where b is greater than or equal to a + 14.	H49140, H50139, N91808, W17361, W23877, W25195, W31242, AA116089, AA116090, AA150544, AA150853, AA417973, AA418133, AA279993, AA280052, AA583751, AA587199, AA618421, AA814427, AA830028, AA916097, AA961686, AA974254, AA987758, AI083878, AI085516, N94820, N95456
828947	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 461 of SEQ ID NO:253, b is an integer of 15 to 475, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:253, and where b is greater than or equal to a + 14.	
828956	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1710 of SEQ ID NO:254, b is an integer of 15 to 1724, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:254, and where b is greater than or equal to a + 14.	T80047, T80393, H22804, N33236, W55892, AA043830, AA062632, AA069280, AA078770, AA082403, AA101062, AA459984, AA460077, AA501353, AA535081, AA588749, AA577376, AA814781, AA836428, AA876439, AA916459, AA938494
828958	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 292 of SEQ ID NO:255, b is an integer of 15 to 306, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:255, and where b is greater than or equal to a + 14.	
828965	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 876 of SEQ ID NO:256, b is an integer of 15 to 890, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:256, and where b is greater than or equal to a + 14.	T60299, R07493, R02543, R02660, N23126, N26234, N28744, N80029, N92370, W06992, W24565, W56160, AA058766, AA082121, AA102497, AA133193, AA157043, AA181057, AA459909, AA419349, AA428256, AA522732, AA531204, AA588687, AA622529, AA631698, AA687351, AA736613, AA736615, AA743076, AA805965, AA825789, AA873396, AA934548, AA984002

828969	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1145 of SEQ ID NO:257, b is an integer of 15 to 1159, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:257, and where b is greater than or equal to a + 14.	R34277, R35477, R40127, R40127, R56401, R63536, R63587, R68336, R68415, R68416, R68428, R68429, R72408, R72447, R75996, R76825, H00671, H00761, H00909, H00910, H06173, H06437, H67367, H67416, H95558, N21675, N22870, N27226, N30906, N34567, N56770, N62120, N72850, N91825, W03069, W31262, W70204, W75946, AA009777, AA009498, AA081398, AA081947, AA082173, AA082577, AA101142, AA102573, AA102587, AA159158, AA279295, AA279321, AA587132, AA576939, AA720862, AA748173, AA808533, AA878214, AA962702, AA987447, AA987635, AA989319, AA995406, AI031632, N84444, AI097592, C02910, C14651, AA081397, C15440
828971	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 741 of SEQ ID NO:258, b is an integer of 15 to 755, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:258, and where b is greater than or equal to a + 14.	
828973	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 700 of SEQ ID NO:259, b is an integer of 15 to 714, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:259, and where b is greater than or equal to a + 14.	
828980	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 511 of SEQ ID NO:260, b is an integer of 15 to 525, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:260, and where b is greater than or equal to a + 14.	AA171806, AA223318
828984	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2986 of SEQ ID NO:261, b is an integer of 15 to 3000, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID	T80804, T81207, R66564, R79533, H10212, H10266, N47700, N47701, N47714, N47715, W92453, W92454, AA047175, AA057046, AA084865, AA084994, AA085435, AA088196, AA088369, AA102606, AA102637, AA102681, AA129398, AA129437, AA133824, AA133835, AA134870, AA155636,

	NO:261, and where b is greater than or equal to a + 14.	AA155692, AA173150, AA173277, AA181676, AA172185, AA187844, AA188417, AA188720, AA203343, AA223606, AA223765, AA232539, AA253486, AA258817, AA258912, AA418911, AA426576, AA428207, AA282012, AA282185, AA506517, AA581113, AA640599, AA864428, AA872063, AA928645, AA947052, AA983384, W28603, AA640958
828985	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 952 of SEQ ID NO:262, b is an integer of 15 to 966, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:262, and where b is greater than or equal to a + 14.	
828988	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2724 of SEQ ID NO:263, b is an integer of 15 to 2738, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:263, and where b is greater than or equal to a + 14.	T73414, R12106, T66627, T66628, T78284, R16041, R16042, R36860, R37936, R61426, R63310, H40110, H40174, N25567, N30486, N34167, N44865, N52758, N57579, N68031, W04668, W31769, W32476, W32662, AA029481, AA029545, AA215402, AA278628, AA278627, AA282001, AA483843, AA576431, AA659932, AA749063, AA768638, AA768824, AA809759, AA830249, N83750, AI097104
828993	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1506 of SEQ ID NO:264, b is an integer of 15 to 1520, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:264, and where b is greater than or equal to a + 14.	
828995	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1554 of SEQ ID NO:265, b is an integer of 15 to 1568, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:265, and where b is greater than or equal to a + 14.	
829000	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 531 of SEQ ID NO:266, b is an integer of 15 to 545, where both a and b	T84984, H62305, N94075

	correspond to the positions of nucleotide residues shown in SEQ ID NO:266, and where b is greater than or equal to a + 14.	
829005	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 748 of SEQ ID NO:267, b is an integer of 15 to 762, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:267, and where b is greater than or equal to a + 14.	T81847, R31803, R63658, H80178, AA086064, AA730231, AA805602, N84214, AA091994
829009	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1419 of SEQ ID NO:268, b is an integer of 15 to 1433, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:268, and where b is greater than or equal to a + 14.	
829010	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2264 of SEQ ID NO:269, b is an integer of 15 to 2278, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:269, and where b is greater than or equal to a + 14.	
829012	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2519 of SEQ ID NO:270, b is an integer of 15 to 2533, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:270, and where b is greater than or equal to a + 14.	T46984, T46985, T60315, T60340, T91262, T82866, T85699, R18936, R22449, R22501, R44051, R44051, R62350, R62351, R62967, R63021, R67538, R67539, H00265, H00266, H05754, H05861, H17661, H17778, H37895, R84704, R85663, R85705, R92774, H71754, H86241, H86596, N77995, N94481, W23930, W33005, W42716, W42804, W42856, W42911, W48687, W48688, W51894, W60144, AA013165, AA013166, AA016027, AA016116, AA019160, AA019173, AA019737, AA019781, AA019874, AA019940, AA020855, AA021014, AA039946, AA039812, AA044966, AA059316, AA059332, AA062810, AA069688, AA074166, AA074690, AA074819, AA079227, AA086267, AA085941, AA101899, AA111855, AA112207, AA112317, AA113083, AA113110, AA112379, AA128454, AA129184, AA134373, AA134374, AA147440, AA147441, AA147468, AA147469, AA152007, AA182029, AA188388,

		AA193685, AA514744, AA525480, AA553895, AA559119, AA580724, AA595036, AA600916, AA601895, AA602350, AA631450, AA633022, AA640333, AA580604, AA715813, AA806865, AA808711, AA811858, AA833843, AA862552, AA873179, AA878958, AA887089, AA918330, AA922879, AA937320, AA977779, AA987809, AA991856, AA999930, AI081179, W28427, N86448, AA640960, AA641152
829013	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1604 of SEQ ID NO:271, b is an integer of 15 to 1618, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:271, and where b is greater than or equal to a + 14.	R12986, R32825, R32839, R32927, R32942, R40183, R52946, R53730, R40183, R66041, H98989, N52010, N54624, N66635, AA046243, AA149949, AA253362, AA253485, AA258773, AA257971, AA262281, AA422167, AA262911, AA513150, AA687117, AA687257, AA747442, AA748820, AA749108, AA767245, AA806305, AA811958, AA903407, AA937560, AA938330, AA976840, AA094074
829019	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 456 of SEQ ID NO:272, b is an integer of 15 to 470, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:272, and where b is greater than or equal to a + 14.	
829020	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 969 of SEQ ID NO:273, b is an integer of 15 to 983, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:273, and where b is greater than or equal to a + 14.	AA136693, AA136791, AA233217, AA419607
829021	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1992 of SEQ ID NO:274, b is an integer of 15 to 2006, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:274, and where b is greater than or equal to a + 14.	T94357, T94712, R12024, R12980, R37092, R40178, R40178, H06066, H13404, N70651, W06945, N90742, AA071520, AA082342, AA086292, AA111847, AA508760, AA513083, AA513134, AA975983, AA987297, N86943
829026	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1362 of	R46780, R56425, H14131, H14048, H19990, H44884, W73060, W76648, AA258220, AA732283, AA732519, AA748619, AA768036, AA830813

	SEQ ID NO:275, b is an integer of 15 to 1376, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:275, and where b is greater than or equal to a + 14.	
829030	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2580 of SEQ ID NO:276, b is an integer of 15 to 2594, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:276, and where b is greater than or equal to a + 14.	
829035	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 665 of SEQ ID NO:277, b is an integer of 15 to 679, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:277, and where b is greater than or equal to a + 14.	
829041	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1464 of SEQ ID NO:278, b is an integer of 15 to 1478, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:278, and where b is greater than or equal to a + 14.	T64828, R13411, R40922, H17358, AA829407, AA991316
829045	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2307 of SEQ ID NO:279, b is an integer of 15 to 2321, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:279, and where b is greater than or equal to a + 14.	R94934, R95018, R96941, R96998, N62469, N79188, AA056180, AA079122, AA079223, AA190398, AA190542, AA279989, AA280050, AA563719, AA563967, AA621823, AA639374, AA743441, AA809943, AA903777, AA991450, AA091152
829048	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1679 of SEQ ID NO:280, b is an integer of 15 to 1693, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:280, and where b is greater than or equal to a + 14.	
829051	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the	

	general formula of a-b, where a is any integer between 1 to 244 of SEQ ID NO:281, b is an integer of 15 to 258, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:281, and where b is greater than or equal to a + 14.	
829052	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1750 of SEQ ID NO:282, b is an integer of 15 to 1764, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:282, and where b is greater than or equal to a + 14.	T54099, T54192, R42585, R42585, H30486, R83722, N24879, N34365, N36398, W80812, W80905, AA040726, AA040725, AA069816, AA099148, AA099246, AA130358, AA131274, AA143111, AA150578, AA553644, H89452, AA570403, AA985591, AI076032, AA092873
829057	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 785 of SEQ ID NO:283, b is an integer of 15 to 799, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:283, and where b is greater than or equal to a + 14.	R17092
829058	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1475 of SEQ ID NO:284, b is an integer of 15 to 1489, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:284, and where b is greater than or equal to a + 14.	
829059	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 688 of SEQ ID NO:285, b is an integer of 15 to 702, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:285, and where b is greater than or equal to a + 14.	T99023, R54176, H73053, H72832, H73054, H80706, AA988806
829061	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1161 of SEQ ID NO:286, b is an integer of 15 to 1175, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:286, and where b is greater than or equal to a + 14.	
829062	Preferably excluded from the present invention are one or more	

	polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2859 of SEQ ID NO:287, b is an integer of 15 to 2873, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:287, and where b is greater than or equal to a + 14.	
829063	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2090 of SEQ ID NO:288, b is an integer of 15 to 2104, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:288, and where b is greater than or equal to a + 14.	T56853, R13426, R40938, R40938, R56447, H64343, W94129, W94024, W95653, W95654, AA001812, AA158586, AA158585, AA179917, AA463947, AA464082, AA421875, AA430503, AA430622, AA228990, AA506167, AA528459, AA551350, AA564494, AA601544, AA604335, AA622270, AA747745, AA760947, AA827325, AA888125, AA910238
829064	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1237 of SEQ ID NO:289, b is an integer of 15 to 1251, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:289, and where b is greater than or equal to a + 14.	
829066	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1577 of SEQ ID NO:290, b is an integer of 15 to 1591, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:290, and where b is greater than or equal to a + 14.	
829068	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2372 of SEQ ID NO:291, b is an integer of 15 to 2386, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:291, and where b is greater than or equal to a + 14.	
829069	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 969 of SEQ ID NO:292, b is an integer of 15 to 983, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:292, and where b is greater than or equal to a + 14.	AA056484, AA056650, AA742863

829074	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2641 of SEQ ID NO:293, b is an integer of 15 to 2655, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:293, and where b is greater than or equal to a + 14.	R21643, R21965, R23012, R31285, R31896, R32700, R32701, R34083, R62210, R64591, R68873, R73888, R73975, R74184, R74270, R76839, R77200, R77720, R78052, H03147, H03956, H15807, H16106, H39711, H39732, H42156, R98951, N41769, W87673, AA007438, AA007439, AA013075, AA099593, AA156625, AA195656, AA195769, AA236849, AA237048, AA226078, AA526030, AA570236, AA570252, AA766062, AA767497, AA769581, AA827847, AA831416, AA911414, AA938690
829077	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1724 of SEQ ID NO:294, b is an integer of 15 to 1738, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:294, and where b is greater than or equal to a + 14.	R11694, AA031610, AA056352, AA099809, AA190527
829078	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1006 of SEQ ID NO:295, b is an integer of 15 to 1020, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:295, and where b is greater than or equal to a + 14.	
829079	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 670 of SEQ ID NO:296, b is an integer of 15 to 684, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:296, and where b is greater than or equal to a + 14.	AA613454
829085	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1824 of SEQ ID NO:297, b is an integer of 15 to 1838, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:297, and where b is greater than or equal to a + 14.	
829093	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the	T86751, N67573, AA084170, AA482701, AA513177, AA715379

	general formula of a-b, where a is any integer between 1 to 1621 of SEQ ID NO:298, b is an integer of 15 to 1635, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:298, and where b is greater than or equal to a + 14.	
829099	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 854 of SEQ ID NO:299, b is an integer of 15 to 868, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:299, and where b is greater than or equal to a + 14.	AA235899, AA524874, AA588559, AA568363, C18296
829101	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 533 of SEQ ID NO:300, b is an integer of 15 to 547, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:300, and where b is greater than or equal to a + 14.	N28457
829102	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 851 of SEQ ID NO:301, b is an integer of 15 to 865, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:301, and where b is greater than or equal to a + 14.	N24654, N35441, N72250, W00539, W44692, AA101155, AA491668, AI054009, AI054199, W38644
829103	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 801 of SEQ ID NO:302, b is an integer of 15 to 815, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:302, and where b is greater than or equal to a + 14.	R34801, N36324, D81161, D81435, C15688, C15742
829104	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1905 of SEQ ID NO:303, b is an integer of 15 to 1919, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:303, and where b is greater than or equal to a + 14.	R08917, R09023, T95465, R07005, R19551, R37796, R43901, R43901, R65802, R65897, R77267, R77316, R82856, R82857, H15156, H15216, R93133, H77582, H77583, N45210, N50021, N55569, N58316, N59861, N59869, N76954, N77681, N93112, W38788, W52631, AA011659, AA011707, AA043405, AA133302, AA133248, AA134238, AA134239, AA150954, AA151044, AA459974, AA460066, AA503364, AA522740,

		AA522866, AA523791, AA602932, AA602716, AA876807, AA877039, AA879223, AA923007, AA935208, AI082642, AI094830
829109	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 143 of SEQ ID NO:304, b is an integer of 15 to 157, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:304, and where b is greater than or equal to a + 14.	
829111	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 329 of SEQ ID NO:305, b is an integer of 15 to 343, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:305, and where b is greater than or equal to a + 14.	
829115	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 682 of SEQ ID NO:306, b is an integer of 15 to 696, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:306, and where b is greater than or equal to a + 14.	AA064674, AA078775
829116	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 382 of SEQ ID NO:307, b is an integer of 15 to 396, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:307, and where b is greater than or equal to a + 14.	
829119	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 535 of SEQ ID NO:308, b is an integer of 15 to 549, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:308, and where b is greater than or equal to a + 14.	T51849, T51895, R31503, H89196, W94076, AA233517, AA557320, AA582238, AA604556, AA659141
829120	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the	

	general formula of a-b, where a is any integer between 1 to 1764 of SEQ ID NO:309, b is an integer of 15 to 1778, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:309, and where b is greater than or equal to a + 14.	
829121	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 757 of SEQ ID NO:310, b is an integer of 15 to 771, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:310, and where b is greater than or equal to a + 14.	T79424, T86294, T98674, R00295, R41707, R42706, R45491, R46655, R41707, R42706, R45491, R46655, R56768, R71860, R71861, H17970, N55536, N80100, W46264, W46265, W46263, W72406, W73710, W76436, AA133997, AA470389, AA514398, AA524707, AA536170, F15823, AA731228, AA766110, AA825368, AA828215, AA833768, AA837103, AA918015, AA988068, AA999844, W46262, C04804, AA062584, AA082539
829123	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1405 of SEQ ID NO:311, b is an integer of 15 to 1419, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:311, and where b is greater than or equal to a + 14.	T53735, T53833, T73419, T79418, T79419, AA035245, AA530898, AA588281, AA631068, C01039
829126	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 512 of SEQ ID NO:312, b is an integer of 15 to 526, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:312, and where b is greater than or equal to a + 14.	
829135	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2421 of SEQ ID NO:313, b is an integer of 15 to 2435, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:313, and where b is greater than or equal to a + 14.	
829136	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2529 of SEQ ID NO:314, b is an integer of 15 to 2543, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:314, and where b is greater than or equal to a + 14.	N24451, N54675, AA135096, AA164383, AA180531, AA180520, AA179618, AA180509, C17250

829138	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 814 of SEQ ID NO:315, b is an integer of 15 to 828, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:315, and where b is greater than or equal to a + 14.	T57569, T86491, R00162, R00163, R91950, R92281, R93566, R93567, R98556, R98557, H82687, N23234, N23249, N27394, N40804, N52001, N54610, N62258, N69979, N79347, N98581, N98559, W24241, W30694, W39016, W49542, W49773, W93332, W95036, N90230, AA015762, AA022871, AA022872, AA151308, AA151309, AA203551, AA461104, AA424178, AA424202, AA467853, AA467908, AA513455, AA564159, AA576516, AA579461, AA740779, AA865373, AA938596, AA972781, AA641536, AA092083
829142	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1594 of SEQ ID NO:316, b is an integer of 15 to 1608, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:316, and where b is greater than or equal to a + 14.	
829148	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1043 of SEQ ID NO:317, b is an integer of 15 to 1057, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:317, and where b is greater than or equal to a + 14.	T70817, H97087, N28699, N59032, W31740, W63702
829149	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1322 of SEQ ID NO:318, b is an integer of 15 to 1336, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:318, and where b is greater than or equal to a + 14.	T57875, AA062633, AA180493, AA255651, AA815168, AA827196, AA988896, AI032193
829156	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 482 of SEQ ID NO:319, b is an integer of 15 to 496, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:319, and where b is greater than or equal to a + 14.	
829162	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the	W28213, C20991

	general formula of a-b, where a is any integer between 1 to 1742 of SEQ ID NO:320, b is an integer of 15 to 1756, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:320, and where b is greater than or equal to a + 14.	
829170	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 574 of SEQ ID NO:321, b is an integer of 15 to 588, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:321, and where b is greater than or equal to a + 14.	T54688
829177	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 724 of SEQ ID NO:322, b is an integer of 15 to 738, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:322, and where b is greater than or equal to a + 14.	
829179	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 862 of SEQ ID NO:323, b is an integer of 15 to 876, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:323, and where b is greater than or equal to a + 14.	
829184	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1308 of SEQ ID NO:324, b is an integer of 15 to 1322, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:324, and where b is greater than or equal to a + 14.	
829185	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 328 of SEQ ID NO:325, b is an integer of 15 to 342, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:325, and where b is greater than or equal to a + 14.	
829188	Preferably excluded from the present invention are one or more	T58653, T58703, T75221, T77245, T77461, R09770, R10874,

	polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3676 of SEQ ID NO:326, b is an integer of 15 to 3690, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:326, and where b is greater than or equal to a + 14.	R10923, T78618, R05603, R12362, R13912, R23445, R26046, R37744, R39442, R43682, R44004, R43682, R44004, H27016, H50941, H51605, H52497, N23353, N28825, N35021, N45029, N52865, N93751, N94155, W67224, W67334, W78117, W79824, W94552, W92625, AA036842, AA040393, AA040497, AA074284, AA075940, AA135258, AA157449, AA159938, AA188822, AA188883, AA223533, AA280881, AA280961, AA515694, AA573708, AA720966, AA730134, AA761564, AA805432, AA826208, AA831736, AA833940, AA834312, AA888244, AA911536, AA918643, AA922815, AA932119, AA933022
829190	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 705 of SEQ ID NO:327, b is an integer of 15 to 719, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:327, and where b is greater than or equal to a + 14.	
829193	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 975 of SEQ ID NO:328, b is an integer of 15 to 989, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:328, and where b is greater than or equal to a + 14.	AA043829
829196	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 420 of SEQ ID NO:329, b is an integer of 15 to 434, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:329, and where b is greater than or equal to a + 14.	AA156138
829197	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 682 of SEQ ID NO:330, b is an integer of 15 to 696, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:330, and where b is greater than or equal to a + 14.	R13055

829202	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 527 of SEQ ID NO:331, b is an integer of 15 to 541, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:331, and where b is greater than or equal to a + 14.	
829203	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 291 of SEQ ID NO:332, b is an integer of 15 to 305, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:332, and where b is greater than or equal to a + 14.	
829209	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 431 of SEQ ID NO:333, b is an integer of 15 to 445, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:333, and where b is greater than or equal to a + 14.	H96926
829210	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 303 of SEQ ID NO:334, b is an integer of 15 to 317, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:334, and where b is greater than or equal to a + 14.	
829214	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1510 of SEQ ID NO:335, b is an integer of 15 to 1524, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:335, and where b is greater than or equal to a + 14.	T65464, T65607, T65616, R68318, R81279, H19079, H21595, W38816, AA173621, AA195611, AA461025, AA429991, AA281779, AA523034
829215	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 292 of SEQ ID NO:336, b is an integer of 15 to 306, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID	

	NO:336, and where b is greater than or equal to a + 14.	
829219	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 277 of SEQ ID NO:337, b is an integer of 15 to 291, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:337, and where b is greater than or equal to a + 14.	
829220	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1250 of SEQ ID NO:338, b is an integer of 15 to 1264, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:338, and where b is greater than or equal to a + 14.	T91056, R08770, R10337, T85922, R08771, N30353, N33349, N34024, N36835, N43012, N46055, N46938, N47028, N48163, N53309, N55453, N57768, N59733, N62846, N70614, N76825, N77753, W04936, W46253, W57556, W80670, W88648, AA081410, AA233146, AA251750, AA485043, AA554001, AA628055, AA632073, AA632104, AA576915, AA814024, AA829780, AA887202, AA902514, AA927412, AI056152, AI085313, AI084094
829222	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 745 of SEQ ID NO:339, b is an integer of 15 to 759, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:339, and where b is greater than or equal to a + 14.	T53949, T55484, T55410, N57462, N93015, W21365, W88723, AA025365, AA081355, AA081356, AA418410, AA418507, AA422027, AA593855, AA593915, AA639807, AA814928, AA833745, AA872346, AA887280, AA904054, AA090282
829223	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2625 of SEQ ID NO:340, b is an integer of 15 to 2639, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:340, and where b is greater than or equal to a + 14.	T39922, N73780, N74186, N99401, W49823, AA026960, AA028073, AA418303, AA418345, AA425606, AA425545, AA426176, AA279347, AA492172, AA587366, AA621961, AA621973, AA834751, AA641513
829225	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1810 of SEQ ID NO:341, b is an integer of 15 to 1824, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:341, and where b is greater than or equal to a + 14.	T64318, T65668, AA016241, AA173963, AA618544
829226	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the	R17300, R31023, R61393, R61438, R61703, R61704, R72584, R72589, R74189, R74276, R78679, H20944, H22649, H39794,

	general formula of a-b, where a is any integer between 1 to 4517 of SEQ ID NO:342, b is an integer of 15 to 4531, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:342, and where b is greater than or equal to a + 14.	R84924, H79108, H79109, H81746, H81747, N32103, N38733, N45414, N47287, N47868, N48370, N48604, N50820, N51222, W19758, W38435, W44825, W74326, AA031730, AA045438, AA046531, AA047110, AA047266, AA148821, AA150421, AA169649, AA169829, AA169806, AA169813, AA171644, AA171651, AA227734, AA228119, AA255720, AA258153, AA424351, AA424866, AA426160, AA281120, AA281932, AA594385, AA594783, AA627918, AA570350, AA744689, AA748507, AA805709, AA806075, AA805170, AA865268, AA872935, AA876562, AA911965, AA916659, AA917349, AA918770, AA918850, AA946925, D81172, D81397, D78876, C01437, N86700, N88264, C05670, C18759
829227	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 570 of SEQ ID NO:343, b is an integer of 15 to 584, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:343, and where b is greater than or equal to a + 14.	T47087, T47086, R44450, R44450, H13259, H95459, AA035630, AA179511, AA418751, AA527136, AA961714, AA992449
829231	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 764 of SEQ ID NO:344, b is an integer of 15 to 778, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:344, and where b is greater than or equal to a + 14.	
829232	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3726 of SEQ ID NO:345, b is an integer of 15 to 3740, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:345, and where b is greater than or equal to a + 14.	N26050, N40415, N41638, AA001329, AA001916, AA158802, AA158803, AA213393, AA213394, AA213538, AA424282, AA459213, AA482209, AA482297, AA580754, AA729270, AA737966, AA742269, AA804199, AA937087, N33467, N43860, C02233
829233	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 432 of SEQ ID NO:346, b is an integer of 15 to 446, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID	

	NO:346, and where b is greater than or equal to a + 14.	
829239	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 768 of SEQ ID NO:347, b is an integer of 15 to 782, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:347, and where b is greater than or equal to a + 14.	
829240	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 425 of SEQ ID NO:348, b is an integer of 15 to 439, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:348, and where b is greater than or equal to a + 14.	
829242	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2342 of SEQ ID NO:349, b is an integer of 15 to 2356, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:349, and where b is greater than or equal to a + 14.	T91514, T91542, T94168, T78752, R14281, R31952, R32000, R37970, R37971, R39326, R40572, R40572, R55803, R55886, R66639, R81490, R81731, H53614, H53652, H87392, H97030, N26679, N35814, N39832, N64783, N76195, N92867, N95188, W21546, W25593, W61031, W78096, W79455, AA022610, AA022611, AA034251, AA063637, AA102635, AA102677, AA171440, AA190925, AA191317, AA223281, AA223381, AA226876, AA227079, AA460842, AA461146, AA428884, AA429051, AA429588, AA430105, AA526857, AA534144, AA542854, AA542868, AA554978, AA582495, AA605088, AA614111, AA614129, AA635924, AA580535, AA732502, AA740954, AA812350, AA827279, AA857515, AA928973, AA985646, AA995666, AI015556, U47719, N85053, C02475, C14936, C20619
829246	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1205 of SEQ ID NO:350, b is an integer of 15 to 1219, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:350, and where b is greater than or equal to a + 14.	
829250	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the	

	general formula of a-b, where a is any integer between 1 to 394 of SEQ ID NO:351, b is an integer of 15 to 408, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:351, and where b is greater than or equal to a + 14.	
829253	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1269 of SEQ ID NO:352, b is an integer of 15 to 1283, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:352, and where b is greater than or equal to a + 14.	
829256	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3215 of SEQ ID NO:353, b is an integer of 15 to 3229, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:353, and where b is greater than or equal to a + 14.	R17284, R17354, R17854, R24590, R33671, R33788, R35944, R36246, R36247, R36926, R43105, R44395, R49460, R49460, R44395, R43105, H24440, H24469, H82721, H83591, N50755, N55574, N64383, N92180, N90817, AA019697, AA026244, AA026441, AA037458, AA037544, AA127492, AA127587, AA190907, AA243225, AA243269, AA279209, AA503849, AA507466, AA639522, AA731780, AA736864, AA766007, AA090592
829263	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 492 of SEQ ID NO:354, b is an integer of 15 to 506, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:354, and where b is greater than or equal to a + 14.	N41747
829266	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 728 of SEQ ID NO:355, b is an integer of 15 to 742, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:355, and where b is greater than or equal to a + 14.	
829271	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1681 of SEQ ID NO:356, b is an integer of 15 to 1695, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID	T39261, T49204, T72303, T71643, R07380, T66682, T82066, T83481, R01790, R16223, R20708, R81714, H06087, H09039, H46863, R96294, H50808, H84189, H84190, H84400, H91054, H91348, H96283, N32070, N39797, N45073, N45382, W04773, W21170, W52394, W51822, AA017710, AA017711, AA019476,

	NO:356, and where b is greater than or equal to a + 14.	AA021323, AA021324, AA044865, AA045153, AA054523, AA081533, AA083253, AA084388, AA083588, AA101641, AA101642, AA101720, AA135652, AA136639, AA136846, AA151892, AA179772, AA180489, AA187824, AA188556, AA224078, AA232050, AA232154, AA425968, AA531528, AA581305, AA742833, D83801, D83850, W22420
829273	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 914 of SEQ ID NO:357, b is an integer of 15 to 928, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:357, and where b is greater than or equal to a + 14.	
829274	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1360 of SEQ ID NO:358, b is an integer of 15 to 1374, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:358, and where b is greater than or equal to a + 14.	
829276	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 4138 of SEQ ID NO:359, b is an integer of 15 to 4152, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:359, and where b is greater than or equal to a + 14.	
829279	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1142 of SEQ ID NO:360, b is an integer of 15 to 1156, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:360, and where b is greater than or equal to a + 14.	
829280	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 362 of SEQ ID NO:361, b is an integer of 15 to 376, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID	

	NO:361, and where b is greater than or equal to a + 14.	
829283	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 505 of SEQ ID NO:362, b is an integer of 15 to 519, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:362, and where b is greater than or equal to a + 14.	
829284	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1371 of SEQ ID NO:363, b is an integer of 15 to 1385, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:363, and where b is greater than or equal to a + 14.	R35022, N53092, W56437, AA425107, AA429328, AA639462
829285	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 963 of SEQ ID NO:364, b is an integer of 15 to 977, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:364, and where b is greater than or equal to a + 14.	T98355, N35799, N68373, AA233837, AA234338, AA541363, C05871, C06442
829287	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 950 of SEQ ID NO:365, b is an integer of 15 to 964, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:365, and where b is greater than or equal to a + 14.	T75573, T75574, T89291, T92020, T92115, R09394, R09395, T81925, T81926, T84370, H15008, H15009, H22443, H22477, H42624, H70914, H70998, H91740, H70914, N21387, N21568, N29475, N31342, N35714, N39243, N46687, N58940, N62219, N62544, N71355, N73001, N79212, N79311, N80035, N92595, N95523, N99823, W02965, W06998, W17066, W17239, W37312, W37553, W38873, W38985, W42735, W42825, W44743, W45210, W60642, W60643, W61216, W72457, W73365, W73442, W73919, W74445, W78073, W94432, W92526, W95225, N89652, N89752, AA034453, AA046851, AA046813, AA053964, AA055047, AA055127, AA074513, AA081359, AA084042, AA098833, AA112180, AA136464, AA165072, AA164675, AA190836, AA255622, AA256734, AA428625, AA484049, AA513283, AA535853, F16222, AA587936, AA614830, AA767121, AA814435, AA832516, AA829611, AA829918, AA872922, AA910970, AA987945, AA988657,

		AA948052, AI094757, D79222, D79845, W79251, C00060
829295	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1283 of SEQ ID NO:366, b is an integer of 15 to 1297, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:366, and where b is greater than or equal to a + 14.	N79069, N94383, AA046494, AA046766, AA101963, AA099652, AA135109, AA135264, AA148582, AA148581, AA150460, AA156662, AA534768, AA557811, AA687147, AA730106, AA810732, AA911850
829296	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 771 of SEQ ID NO:367, b is an integer of 15 to 785, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:367, and where b is greater than or equal to a + 14.	
829297	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 906 of SEQ ID NO:368, b is an integer of 15 to 920, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:368, and where b is greater than or equal to a + 14.	H63163, H69239, AA291944, AA827871, AA995955
829298	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 820 of SEQ ID NO:369, b is an integer of 15 to 834, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:369, and where b is greater than or equal to a + 14.	T85571, T85572, T98605, R06410, R06411, R72558, W25247, W58681, AA126722, AA137218, AA136191, AA531469, AA565025, AA948354, AA978354, AA988766, AI057145, N95214
829302	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 933 of SEQ ID NO:370, b is an integer of 15 to 947, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:370, and where b is greater than or equal to a + 14.	T65369, R16190, R51781, H70499, AA203397
829304	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2326 of SEQ ID NO:371, b is an integer of 15 to 2340, where both a and b	

	correspond to the positions of nucleotide residues shown in SEQ ID NO:371, and where b is greater than or equal to a + 14.	
829320	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1561 of SEQ ID NO:372, b is an integer of 15 to 1575, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:372, and where b is greater than or equal to a + 14.	T83172, T83188, T98062, H14392, AA196911, AA514594
829322	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1864 of SEQ ID NO:373, b is an integer of 15 to 1878, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:373, and where b is greater than or equal to a + 14.	
829355	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 832 of SEQ ID NO:374, b is an integer of 15 to 846, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:374, and where b is greater than or equal to a + 14.	
829364	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 643 of SEQ ID NO:375, b is an integer of 15 to 657, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:375, and where b is greater than or equal to a + 14.	R10800, H79360, AA130522
829919	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 681 of SEQ ID NO:376, b is an integer of 15 to 695, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:376, and where b is greater than or equal to a + 14.	
829941	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3596 of	

	SEQ ID NO:377, b is an integer of 15 to 3610, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:377, and where b is greater than or equal to a + 14.	
829945	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 209 of SEQ ID NO:378, b is an integer of 15 to 223, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:378, and where b is greater than or equal to a + 14.	
829946	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 795 of SEQ ID NO:379, b is an integer of 15 to 809, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:379, and where b is greater than or equal to a + 14.	AA288019, AA502347, AA904261
829947	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2536 of SEQ ID NO:380, b is an integer of 15 to 2550, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:380, and where b is greater than or equal to a + 14.	T66737, T66738, T74003, T77189, T80326, R13808, R14624, R15371, R16290, R19838, R21469, R24972, R37667, R38092, R39443, R39761, R40215, R40379, R42113, R45233, R42113, R42856, R40215, R40379, R45233, R45937, R56287, R59950, R59951, R60203, R60436, H09760, H09845, H10702, H10703, H19185, H29333, H29426, N94574, W30864, W45066, W45179, W47249, W47622, W47621, W73903, W74765, W95498, W95585, AA039360, AA039359, AA043667, AA057482, AA083653, AA088919, AA131592, AA135473, AA135544, AA147364, AA147416, AA161437, AA164913, AA165378, AA164333, AA181099, AA430483, AA281878, AA291947, AA493956, AA582300, AA740445, AA743497, AA875945, AA878761, AA923149, AA931525, AA931950, AA935699, AA947521, AA962775, AA977566, AA984017, AA988746, AI095060, D82399, W25818, W51914, C15840
829952	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1254 of SEQ ID NO:381, b is an integer of 15 to 1268, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID	R17678, R26888, R27120, R35870, R35871, R51276, R66882, R67967, H27381, H28345, H38579, R93605, R97908, R97907, H53653, H61431, H61432, H62657, H63776, H63826, H65287, H65810, H89508, H89654, N74909, W23437, AA026270, AA026558, AA177150, AA515407, AA527495, AA535324,

	NO:381, and where b is greater than or equal to a + 14.	AA594129, AA568558, AA864390, AA999878, AI014459, AI017407, AI017824
829954	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 840 of SEQ ID NO:382, b is an integer of 15 to 854, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:382, and where b is greater than or equal to a + 14.	
829955	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1077 of SEQ ID NO:383, b is an integer of 15 to 1091, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:383, and where b is greater than or equal to a + 14.	T47229, T47230, R02311, R43154, R51528, R43154, H42209, R88215, N49583, N93033, W21271, W31966, AA029149, AA513795, AA548358, AA612791, AA633375, AA830042, AA917951, N83314, N86243, C02678
829957	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1015 of SEQ ID NO:384, b is an integer of 15 to 1029, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:384, and where b is greater than or equal to a + 14.	T39589, T40683, H47643, R92700, R99102, R99644, H53816, H58333, H58722, H61989, H61990, H63765, H63809, H73313, H73501, N38910, N46484, N66604, N69475, N75847, W01771, W07430, W74706, W74743, W87451, W87550, N90967, AA010671, AA011259, AA026367, AA026459, AA063538, AA133609, AA157688, AA157767, AA252640, AA262927, AA417991, AA418050, AA425054, AA429232, AA505081, AA602637, AA569939, AA688193, AA714567, AA715109, AA721733, AA761769, AA824602, AA829416, AA910995, AA932302, AA934664, AA960927, AA973923, AI002231, AI094664
829958	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 569 of SEQ ID NO:385, b is an integer of 15 to 583, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:385, and where b is greater than or equal to a + 14.	W31195, W38586, N90200, AA045674, AA045675, AA064826, AA064769, AA082177, AA129757, AA133252, AA187005, AA188378, AA226394, AA491262, AA523135, AA527421, AA527902, AA533279, AA554691, AA632078, AA721457, AA743821, AA760765, AA766192, AA769476, AA805805, AA815094, AA826696, AA873340, AA876652, AA902562, AA935370, AA091473
829960	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2396 of	T87492, T89410, T89773, T80188, T83347, T83577, T85604, T86095, H44324, R86738, R86745, R87175, R87176, R93579, R97628, H59234, H67776, H69384, H89665, H90369, H91278,

	SEQ ID NO:386, b is an integer of 15 to 2410, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:386, and where b is greater than or equal to a + 14.	H93827, N59685, N73235, N77230, N99493, W01516, W07398, W07499, AA011532, AA127663, AA127842, AA127871, AA131770, AA131783, AA203697, AA223149, AA657524, AA770678, AA828971, AA937743
829966	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 675 of SEQ ID NO:387, b is an integer of 15 to 689, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:387, and where b is greater than or equal to a + 14.	T94747, T91932, R10556, T95267, T95268, H90557, N59601, W02671, W03166, AA523419
829967	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 784 of SEQ ID NO:388, b is an integer of 15 to 798, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:388, and where b is greater than or equal to a + 14.	T66815, T66816, T90190, R07384, T81628, T81788, T82103, T83000, R23462, R25324, R26060, R31477, R31478, R66771, R80777, R80976, H13673, H13721, R98517, H92094, H94096, H94097, N30791, N31967, N32621, N41566, N47840, N57286, N75841, W07482, W16880, W46399, W46507, W72152, W77912, AA040326, AA040305, AA147001, AA147002, AA176399, AA178863, AA188782, AA188633, AA502400, AA503270, AA508898, AA515395, AA557399, AA610193, AA714481, AA740261, AA748847, AA760659, AA766512, AA824416, AA877577, AA910372, AA938717, AI018625, AI056489, N92492, AI084101, AA642564
829970	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1677 of SEQ ID NO:389, b is an integer of 15 to 1691, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:389, and where b is greater than or equal to a + 14.	W57592, AA253247
829981	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 440 of SEQ ID NO:390, b is an integer of 15 to 454, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:390, and where b is greater than or equal to a + 14.	N44941
829985	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the	T58690, H10115, AA101544, AA171779, AA173847

	general formula of a-b, where a is any integer between 1 to 793 of SEQ ID NO:391, b is an integer of 15 to 807, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:391, and where b is greater than or equal to a + 14.	
829986	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 913 of SEQ ID NO:392, b is an integer of 15 to 927, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:392, and where b is greater than or equal to a + 14.	R72689, H39575, AA516440, AA662417
829988	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1009 of SEQ ID NO:393, b is an integer of 15 to 1023, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:393, and where b is greater than or equal to a + 14.	
829990	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 808 of SEQ ID NO:394, b is an integer of 15 to 822, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:394, and where b is greater than or equal to a + 14.	
829991	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1688 of SEQ ID NO:395, b is an integer of 15 to 1702, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:395, and where b is greater than or equal to a + 14.	N22386, AA461107, AA493109, AA932044, AA976154, AA995814
829992	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 844 of SEQ ID NO:396, b is an integer of 15 to 858, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:396, and where b is greater than or equal to a + 14.	W44338, W44452, AA600841, AA577032, AA936480, AA973451
829993	Preferably excluded from the present invention are one or more	

	polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1096 of SEQ ID NO:397, b is an integer of 15 to 1110, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:397, and where b is greater than or equal to a + 14.	
829998	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 850 of SEQ ID NO:398, b is an integer of 15 to 864, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:398, and where b is greater than or equal to a + 14.	R12950, R56786, H09888, H91803
829999	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 257 of SEQ ID NO:399, b is an integer of 15 to 271, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:399, and where b is greater than or equal to a + 14.	
830000	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 911 of SEQ ID NO:400, b is an integer of 15 to 925, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:400, and where b is greater than or equal to a + 14.	
830001	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1071 of SEQ ID NO:401, b is an integer of 15 to 1085, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:401, and where b is greater than or equal to a + 14.	
830005	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 334 of SEQ ID NO:402, b is an integer of 15 to 348, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:402, and where b is greater than or equal to a + 14.	

830009	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1456 of SEQ ID NO:403, b is an integer of 15 to 1470, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:403, and where b is greater than or equal to a + 14.	
830010	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2473 of SEQ ID NO:404, b is an integer of 15 to 2487, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:404, and where b is greater than or equal to a + 14.	
830127	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1242 of SEQ ID NO:405, b is an integer of 15 to 1256, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:405, and where b is greater than or equal to a + 14.	T80487, R61657
830128	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 757 of SEQ ID NO:406, b is an integer of 15 to 771, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:406, and where b is greater than or equal to a + 14.	
830129	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2629 of SEQ ID NO:407, b is an integer of 15 to 2643, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:407, and where b is greater than or equal to a + 14.	T53792, T53907, T53943, T62085, T62142, R20454, R78770, R78927, R79027, R79077, H98608, N48338, N49063, W01400, W52282, W57571, AA035258, AA035470, AA101541, AA114162, AA121802, AA129334, AA129628, AA130575, AA130988, AA131026, AA156750, AA156922, AA157263, AA157360, AA223729, AA223816, AA489148, AA490861, AA516421, AA526784, AA533164, AA535426, AA552972, AA583471, AA605156, AA575994, AA747160, AA804291, AA887994, AA937881, AA948245, AA974518, AA974784, AI002302, AI051153, N84559, N86782, AA642578, AA093419
830137	Preferably excluded from the present invention are one or more	

	polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1632 of SEQ ID NO:408, b is an integer of 15 to 1646, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:408, and where b is greater than or equal to a + 14.	
830140	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 862 of SEQ ID NO:409, b is an integer of 15 to 876, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:409, and where b is greater than or equal to a + 14.	
830157	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1836 of SEQ ID NO:410, b is an integer of 15 to 1850, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:410, and where b is greater than or equal to a + 14.	
830195	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 647 of SEQ ID NO:411, b is an integer of 15 to 661, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:411, and where b is greater than or equal to a + 14.	
830196	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1249 of SEQ ID NO:412, b is an integer of 15 to 1263, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:412, and where b is greater than or equal to a + 14.	T47007, T47008, T59996, T63678, T72979, T73043, R20327, R34736, H18043, H69946, H98876, W79567, AA069850, AA070319, AA074422, AA076309, AA081601, AA101958, AA113902, AA126400, AA134002, AA134658, AA134640, AA135254, AA146731, AA155584, AA157966, AA159110, AA159386, AA159466, AA160637, AA179462, AA182917, AA182648, AA190534, AA220918, AA223557, AA227300, AA232517, AA233585, AA932527, N83710, N85080, W28216, W28475, W28650, AA090479
830409	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1323 of	

	SEQ ID NO:413, b is an integer of 15 to 1337, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:413, and where b is greater than or equal to a + 14.	
830417	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 778 of SEQ ID NO:414, b is an integer of 15 to 792, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:414, and where b is greater than or equal to a + 14.	T70867, R12290, T78032, T80453, T80532, R12432, R12507, R18857, R23505, R51536, R52975, R53640, H12996, H22829, H63914, H64034, H71775, H85810, H97709, N42249, W39175, AA018531, AA018491, AA018481, AA052919, AA079678, AA083267, AA102444, AA127022, AA147778, AA226551, AA994837, N84172, W95500, C02827, C04397, AA090040
830531	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1328 of SEQ ID NO:415, b is an integer of 15 to 1342, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:415, and where b is greater than or equal to a + 14.	
830677	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1099 of SEQ ID NO:416, b is an integer of 15 to 1113, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:416, and where b is greater than or equal to a + 14.	
831355	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1160 of SEQ ID NO:417, b is an integer of 15 to 1174, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:417, and where b is greater than or equal to a + 14.	
831420	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 659 of SEQ ID NO:418, b is an integer of 15 to 673, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:418, and where b is greater than or equal to a + 14.	
831702	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the	

	general formula of a-b, where a is any integer between 1 to 2164 of SEQ ID NO:419, b is an integer of 15 to 2178, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:419, and where b is greater than or equal to a + 14.	
831717	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1870 of SEQ ID NO:420, b is an integer of 15 to 1884, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:420, and where b is greater than or equal to a + 14.	
832488	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 608 of SEQ ID NO:421, b is an integer of 15 to 622, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:421, and where b is greater than or equal to a + 14.	
833207	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1271 of SEQ ID NO:422, b is an integer of 15 to 1285, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:422, and where b is greater than or equal to a + 14.	
835940	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 514 of SEQ ID NO:423, b is an integer of 15 to 528, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:423, and where b is greater than or equal to a + 14.	
836953	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3104 of SEQ ID NO:424, b is an integer of 15 to 3118, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:424, and where b is greater than or equal to a + 14.	
837105	Preferably excluded from the present invention are one or more	

	polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1396 of SEQ ID NO:425, b is an integer of 15 to 1410, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:425, and where b is greater than or equal to a + 14.	
837300	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1408 of SEQ ID NO:426, b is an integer of 15 to 1422, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:426, and where b is greater than or equal to a + 14.	R22778, H06717, H18453, H26987, H26988, N33207, N44745, W57874, W58145, AA040435, AA278615, AA507344, AA558666, AA578863, AA872443, AA877052, AA877120, AA879047, AA887537, AA910397, AA931214, AI025125, AA040434
837373	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 816 of SEQ ID NO:427, b is an integer of 15 to 830, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:427, and where b is greater than or equal to a + 14.	R21137, H67522, AA081145, AA082099, AA082371, AA130000, AA130415, AA130417, AA132638, AA136918, AA147401, AA157404, AA186519, AA186340, AA186565, AA190900, AA191038, AA190612, AA224065, AA469308, AA514706, AA640391, AA659609, AA814425, AA932379, AA961224, AA974800, AA977316, AI002396, N83374, N83520, N83658, N83770, N85953, N85954, N86486, N86566, N86680, N87938, N88164, N89316, C14148, C14189, AA095113, AA206109
837687	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1608 of SEQ ID NO:428, b is an integer of 15 to 1622, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:428, and where b is greater than or equal to a + 14.	
837991	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 534 of SEQ ID NO:429, b is an integer of 15 to 548, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:429, and where b is greater than or equal to a + 14.	
838442	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 555 of SEQ ID NO:430, b is an integer of 15 to 569, where both a and b	

	correspond to the positions of nucleotide residues shown in SEQ ID NO:430, and where b is greater than or equal to a + 14.	
840541	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 535 of SEQ ID NO:431, b is an integer of 15 to 549, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:431, and where b is greater than or equal to a + 14.	AA205009, AA471299
840543	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1207 of SEQ ID NO:432, b is an integer of 15 to 1221, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:432, and where b is greater than or equal to a + 14.	
840550	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1101 of SEQ ID NO:433, b is an integer of 15 to 1115, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:433, and where b is greater than or equal to a + 14.	T53643, T53644, R67842, R67843, R79329, H12321, H40510, R83261, R88722, R90978, R97638, H51690, H52190, H78699, H89714, N58070, N69832, N98971, AA251228, AA251227, AA282101, AA513006, AA528240, AA558167, AA593383, AA574200, AA577197, AA765822, AA847143, AA863087, AA931049, AA694054
840563	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1590 of SEQ ID NO:434, b is an integer of 15 to 1604, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:434, and where b is greater than or equal to a + 14.	R38732, R71612, R71613, N24083, N31377, N47304, N48623, W87303, W90742, W90798, AA011634, AA011635, AA253397, AA253501, AA257091, AA257121, AA427877, AA503469, AA565303, AA587449, AA613721, AA740312, C01498, AA434535, AA443422, AA454584, AA677081, AI022365, AI052631, AA693545
840565	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 287 of SEQ ID NO:435, b is an integer of 15 to 301, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:435, and where b is greater than or equal to a + 14.	
840569	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 304 of	

	SEQ ID NO:436, b is an integer of 15 to 318, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:436, and where b is greater than or equal to a + 14.	
840570	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1868 of SEQ ID NO:437, b is an integer of 15 to 1882, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:437, and where b is greater than or equal to a + 14.	AI075277, AA675912, AA675911
840571	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2042 of SEQ ID NO:438, b is an integer of 15 to 2056, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:438, and where b is greater than or equal to a + 14.	T47828, T47852, T64841, T65430, T65510, T72584, R17181, R19667, R34515, R41731, R44453, R49058, R50770, R51812, R41731, R49058, R44453, H11004, H15433, H15488, H28705, H28834, AA515873, AA687085, AA863313, AA903803, AA452278, AA452447, AA781246, AA972396, AA993822, AI002821, T10761, D25941, Z41977, Z40833, Z44675, F01498, F03695, F07749, F11901, F12192, F09548, F09821
840573	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 707 of SEQ ID NO:439, b is an integer of 15 to 721, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:439, and where b is greater than or equal to a + 14.	AA149788
840574	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1027 of SEQ ID NO:440, b is an integer of 15 to 1041, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:440, and where b is greater than or equal to a + 14.	T65588, R40688, R42248, R53793, R53794, R42248, R20733, R40688, R66541, R68438, R68439, R77228, R77229, R77595, H18969, H20988, H21032, H49673, H50064, N72287, N80600, W07440, W40167, AA034401, AA035044, AA035506, AA035555, AA182662, AA182740, AA483608, AA588302, AA602357, AA604612, AA639138, D81410, D81461, D81692, AI097583, C15094, AA404494, AA705982, AI080676, AI095724, F09676
840575	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1981 of SEQ ID NO:441, b is an integer of 15 to 1995, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID	W68038, W93774

	NO:441, and where b is greater than or equal to a + 14.	
840579	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1709 of SEQ ID NO:442, b is an integer of 15 to 1723, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:442, and where b is greater than or equal to a + 14.	R25715, R72972, N42280, N99672, AA046377, AA112337, AA137170, AA156083, AA156289, AA234550, AA236661, AA251743, AA256954, AA256645, AA704119, AI073518, AA773818
840580	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1885 of SEQ ID NO:443, b is an integer of 15 to 1899, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:443, and where b is greater than or equal to a + 14.	
840581	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 416 of SEQ ID NO:444, b is an integer of 15 to 430, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:444, and where b is greater than or equal to a + 14.	
840605	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2139 of SEQ ID NO:445, b is an integer of 15 to 2153, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:445, and where b is greater than or equal to a + 14.	T58718, R60700, R60701, H30380, H30430, N42386, AA126493, AA126620, AA128024, AA128067, AA236455, AA234073, AA470382, AA503709, AA635761, AA573225, AA573330, AA659473, AA807615, AA824445, AA825364, AA888670, AA931858, AA935053, AA968889, AA971410, AA973830, AA974807, AA977019, AA991272, AA975535, C02768, AA094041, AA478779, AA478898, AA487854, AA777751, AA845416, AA969094, AI027197, AI027391, AI093994, AI094088, T24618, T25054, Z41574
840607	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 478 of SEQ ID NO:446, b is an integer of 15 to 492, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:446, and where b is greater than or equal to a + 14.	
840609	Preferably excluded from the present invention are one or more	

	polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1525 of SEQ ID NO:447, b is an integer of 15 to 1539, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:447, and where b is greater than or equal to a + 14.	
840610	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3969 of SEQ ID NO:448, b is an integer of 15 to 3983, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:448, and where b is greater than or equal to a + 14.	
840611	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1163 of SEQ ID NO:449, b is an integer of 15 to 1177, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:449, and where b is greater than or equal to a + 14.	
840612	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2414 of SEQ ID NO:450, b is an integer of 15 to 2428, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:450, and where b is greater than or equal to a + 14.	
840615	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2471 of SEQ ID NO:451, b is an integer of 15 to 2485, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:451, and where b is greater than or equal to a + 14.	T65122, T65191, R32009, R32056, R69507, R70398, H06201, R94284, R94634, H51636, H92705, H99325, N24056, N26430, N35932, N39594, N46740, N70376, W88440, AA017294, AA115093, AA115094, AA171679, AA173604, AA173857, AA233061, AA243856, AA279997, AA419480, AA419595, AA536095, AA583207, AA588657, AA604241, AA639870, AA713580, AA714906, AA730848, AA741161, AA832122, AA879136, AA903032, AA938350, AA948280, AA976706, W05017, AA171795, AA401642, AA405839, AA411823, AA628174, AA725876, AA725882, AA833521, AA954549, AA992844, AI014611, AI018081, AI024440, AI025063, AI049677, AI085041, AI090013, AI091784, F11915, F09562,

		AA699825
840622	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 949 of SEQ ID NO:452, b is an integer of 15 to 963, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:452, and where b is greater than or equal to a + 14.	
840623	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 590 of SEQ ID NO:453, b is an integer of 15 to 604, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:453, and where b is greater than or equal to a + 14.	AA248685
840624	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1903 of SEQ ID NO:454, b is an integer of 15 to 1917, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:454, and where b is greater than or equal to a + 14.	N38891, N54665, N45221, F13612, F13702
840631	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1524 of SEQ ID NO:455, b is an integer of 15 to 1538, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:455, and where b is greater than or equal to a + 14.	
840632	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2175 of SEQ ID NO:456, b is an integer of 15 to 2189, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:456, and where b is greater than or equal to a + 14.	H15848, H16160, H27966, H27967, H42798, H87969, N64073, N64076, N64078, AA045740, AA280032, AA280099, AA283727, AA290929, AA814009, AA975514, AI094746, AA449900, AA716758, AA724921, AA860380, AA909482
840633	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1385 of SEQ ID NO:457, b is an integer of 15 to 1399, where both a and b	

	correspond to the positions of nucleotide residues shown in SEQ ID NO:457, and where b is greater than or equal to a + 14.	
840634	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 695 of SEQ ID NO:458, b is an integer of 15 to 709, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:458, and where b is greater than or equal to a + 14.	AA063114
840635	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1269 of SEQ ID NO:459, b is an integer of 15 to 1283, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:459, and where b is greater than or equal to a + 14.	
840636	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 421 of SEQ ID NO:460, b is an integer of 15 to 435, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:460, and where b is greater than or equal to a + 14.	
840637	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 640 of SEQ ID NO:461, b is an integer of 15 to 654, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:461, and where b is greater than or equal to a + 14.	AA001547, AA012848, AA012933, AA017085, AA017194, AA018490, AA810954
840639	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2231 of SEQ ID NO:462, b is an integer of 15 to 2245, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:462, and where b is greater than or equal to a + 14.	
840640	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1266 of	

	SEQ ID NO:463, b is an integer of 15 to 1280, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:463, and where b is greater than or equal to a + 14.	
840650	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2417 of SEQ ID NO:464, b is an integer of 15 to 2431, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:464, and where b is greater than or equal to a + 14.	
840652	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 575 of SEQ ID NO:465, b is an integer of 15 to 589, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:465, and where b is greater than or equal to a + 14.	
840653	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1093 of SEQ ID NO:466, b is an integer of 15 to 1107, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:466, and where b is greater than or equal to a + 14.	
840655	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2183 of SEQ ID NO:467, b is an integer of 15 to 2197, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:467, and where b is greater than or equal to a + 14.	
840659	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3597 of SEQ ID NO:468, b is an integer of 15 to 3611, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:468, and where b is greater than or equal to a + 14.	
840660	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the	AA253121, AA253250

	general formula of a-b, where a is any integer between 1 to 506 of SEQ ID NO:469, b is an integer of 15 to 520, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:469, and where b is greater than or equal to a + 14.	
840661	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 865 of SEQ ID NO:470, b is an integer of 15 to 879, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:470, and where b is greater than or equal to a + 14.	R40087, AA483309, AA720883, AA747744, AA811974, AA853049
840662	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2543 of SEQ ID NO:471, b is an integer of 15 to 2557, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:471, and where b is greater than or equal to a + 14.	R13355, R21688, R23614, R26167, R40871, R46580, R46580, R40871, R67867, R67868, H01101, H01102, H01867, H01868, H02834, H03726, H93708, H95440, H95441, N53845, N66438, N68125, N69039, N73342, AA045604, AA045603, AA101337, AA100423, AA101346, AA101345, AA156296, AA157481, AA158453, AA158452, AA181954, AA187577, AA428908, AA281008, AA281174, AA551925, AA557463, AA588077, AA742447, AA768547, AA814696, AA991197, AI017348, C05887, C06049, AA093441, AA496804, AA599560, AA665699, AA707837, AA775203, AA843259, AA844411, AA889762, AI091389
840663	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 453 of SEQ ID NO:472, b is an integer of 15 to 467, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:472, and where b is greater than or equal to a + 14.	
840670	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1826 of SEQ ID NO:473, b is an integer of 15 to 1840, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:473, and where b is greater than or equal to a + 14.	T71092, T67636, R08286, H13339, H16147, H25692, H38182, R84798, R98981, N79217, W19493, W25579, AA034100, AA056965, AA262921, AA720972, AA768301, AA825825, AA972578, AA094484, AA394311, AA487380, AA778203, AI004258, AI005389, Z39071, Z42947, F02333, F06078, AA682274
840671	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the	R46252, R46252, N49076, W04352, W86176, W86177, W92672, W92692, W93417, AA029831, AA085198, AA464962,

	general formula of a-b, where a is any integer between 1 to 1244 of SEQ ID NO:474, b is an integer of 15 to 1258, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:474, and where b is greater than or equal to a + 14.	AA633124, AA737628, AA737662, AA780382, AA811098, AA836105, AA857959, AA994284, AI076231, C01217, AA780068, AI004350
840672	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 4217 of SEQ ID NO:475, b is an integer of 15 to 4231, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:475, and where b is greater than or equal to a + 14.	
840673	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 677 of SEQ ID NO:476, b is an integer of 15 to 691, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:476, and where b is greater than or equal to a + 14.	
840674	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1404 of SEQ ID NO:477, b is an integer of 15 to 1418, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:477, and where b is greater than or equal to a + 14.	R51915, R54456, R54458, H18062, H18757, W03838, W77892, AA629317, F09686
840677	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1223 of SEQ ID NO:478, b is an integer of 15 to 1237, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:478, and where b is greater than or equal to a + 14.	
840678	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1084 of SEQ ID NO:479, b is an integer of 15 to 1098, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:479, and where b is greater than or equal to a + 14.	T63520, R75617, R75713, R78802, R79103, H25459, H27826, H85479, H85486, H92403, H92620, AA001384, AA001383, AA057832, AA235008, AA253050, AA424651, AA430054, AA430263, AA287947, AA288014, AA481556, AA491320, AA505123, AA548974, AA715297, AA736510, AA747303, AA748308, AA829746, AA909843, AA916866, AA642031, AA211184, AA398153, AA399494, AA477559, AA477676,

		AA782481, AI079168, AI040143, AI080176, AI082310, D12148
840680	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 670 of SEQ ID NO:480, b is an integer of 15 to 684, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:480, and where b is greater than or equal to a + 14.	
840691	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2981 of SEQ ID NO:481, b is an integer of 15 to 2995, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:481, and where b is greater than or equal to a + 14.	T83393, T84298, T84482, R72668, H05782, H06072, H17206, AA199607, AA236200, AA234037, AA256784, AA256492, AA256503, AA256504, AA255526, AA256710, AA424131, AA515794, AA580599, AA748677, AA872189, AA937350, AA995072, C00417, AA451719, AA992171, AI091615, F01634, F05381
840700	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1234 of SEQ ID NO:482, b is an integer of 15 to 1248, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:482, and where b is greater than or equal to a + 14.	N74558, W02490, AA250756, AA721388, AA937643, AA077596, AA633788, AA779964, AA812535, AA912417, AA978273, AA993172, AA993810, D20826
840701	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1848 of SEQ ID NO:483, b is an integer of 15 to 1862, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:483, and where b is greater than or equal to a + 14.	R72545, H77545, H77546, H91001, W46287, W67764, W67765, W72232, W76469, W95399, W95448, AA171990, AA172306, AA193490, AA193486, AA215714, AA481093, AA687382, AA721070, AA731304, AA765386, AA807488, AA830428, AA836173, AA872676, AA903225, AA947751, AA948309, AA679104, AA708104, AA844037, AA773240, AA906091, AI092620
840702	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1650 of SEQ ID NO:484, b is an integer of 15 to 1664, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:484, and where b is greater than or equal to a + 14.	T90642, T83169, R34427, R38259, R46634, R48960, R46634, H08738, H42054, H42099, N55339, N58337, N77345, N77705, W80824, W80945, AA022974, AA045928, AA047535, AA047635, AA129564, AA173541, AA173942, AA189109, AA232209, AA232711, AA256680, AA256679, AA661511, AA877392, AA876721, AA876373, AA977525, W26186, AA045814, AA455935, AA629608, AA456404, AA706605, AA716649, AA716749, AA777167, AA884059, AA910769, AA913276, AI091820, Z30152, Z38891, F05971, F10707

840705	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 955 of SEQ ID NO:485, b is an integer of 15 to 969, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:485, and where b is greater than or equal to a + 14.	
840715	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2558 of SEQ ID NO:486, b is an integer of 15 to 2572, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:486, and where b is greater than or equal to a + 14.	
840717	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1437 of SEQ ID NO:487, b is an integer of 15 to 1451, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:487, and where b is greater than or equal to a + 14.	T79990, R16372, R25837, R32657, R42317, R46835, R53484, R53485, R46835, R42317, R60577, R60630, R71392, R72562, H06281, H06328, H10997, H26530, W71994, W76508, W87458, W87554, AA029771, AA029772, AA039881, AA039966, AA046839, AA047010, AA057673, AA069571, AA069563, AA524160, AA865941, AI017434, AA649997, AA705373, AA776517, AI057398, AI078071, T17221, Z40755, Z45024
840718	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1186 of SEQ ID NO:488, b is an integer of 15 to 1200, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:488, and where b is greater than or equal to a + 14.	
840719	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 271 of SEQ ID NO:489, b is an integer of 15 to 285, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:489, and where b is greater than or equal to a + 14.	
840724	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 668 of SEQ ID NO:490, b is an integer of 15 to 682, where both a and b	

	correspond to the positions of nucleotide residues shown in SEQ ID NO:490, and where b is greater than or equal to a + 14.	
840725	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1845 of SEQ ID NO:491, b is an integer of 15 to 1859, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:491, and where b is greater than or equal to a + 14.	T52811, T52812, R55369, R55607, H29580, H29664, N34553, N59374, N72870, N76477, N78788, N93946, W03090, W03506, W07215, W40445, W99359, W99389, AA031839, AA054995, AA120818, AA232731, AA236542, AA424556, AA424653, AA514847, AA528821, AA564104, AA808072, AA446773, AA449408, AA478629, AA644625, Z38400, Z42136
840727	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2695 of SEQ ID NO:492, b is an integer of 15 to 2709, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:492, and where b is greater than or equal to a + 14.	
840731	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1437 of SEQ ID NO:493, b is an integer of 15 to 1451, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:493, and where b is greater than or equal to a + 14.	R11513, R11731, R12441, R17288, R56469, R60452, H14889, H21054, R85192, H78221, H78227, H78420, H78427, N44642, N50726, N63598, N74649, N79564, W24822, AA121181, AA179753, AA180330, AA210820, AA227204, AA255636, AA687763, AA761335, AA948300, AA203176, AA216635, AA404332, AA434598, AA703138
840733	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1254 of SEQ ID NO:494, b is an integer of 15 to 1268, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:494, and where b is greater than or equal to a + 14.	
840734	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 370 of SEQ ID NO:495, b is an integer of 15 to 384, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:495, and where b is greater than or equal to a + 14.	
840736	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 961 of	W42658, W45183, W78758, W80493, W84630, W84681, W87610, W87901, W94898, W91935, AA484859, AA484987, AA505968, AA640115, AA573309, AA657855, AA659105,

	SEQ ID NO:496, b is an integer of 15 to 975, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:496, and where b is greater than or equal to a + 14.	AA659440, AA715002, AA732364, AA740180, AA742752, AA746960, AA804898, AA825656, AA825665, AA987818, N83465, C14070, AA643844, AA652253, F20803, AA432012, AA678021, AA733050, AA782910, AA846523, AI076183, AI085413, D19829
840737	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2061 [illegible] SEQ ID NO:497, b is an integer of 15 to 2075, where both a and [illegible] correspond to the positions of nucleotide residues shown in SEQ [illegible] NO:497, and where b is greater than or equal to a + 14.	T67132, T67133, T87248, H56042, H56119, N25201, N69014, AA128513, AA129959, AA425701, AA428551, AA911113, AA976370, AA987472, [illegible] .081047, D80388, D80909, D80910, D81505, C1447 [illegible] 2, C14494, C14493, C14495, C14514, C14527, C15539, [illegible] 283123, AA779369, AA773654, AI051187, AI091167, AI093159, T24488, AA694308, AA700909
840739	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1890 of SEQ ID NO:498, b is an integer of 15 to 1904, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:498, and where b is greater than or equal to a + 14.	
840746	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2857 of SEQ ID NO:499, b is an integer of 15 to 2871, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:499, and where b is greater than or equal to a + 14.	R12296, R12807, R16375, R16741, R18738, R38102, R42319, R43498, R44177, R51993, R51994, R43498, R43060, R44177, R42319, H40121, H40275, N22396, N69345, W37333, W38750, AA054559, AA054619, AA131766, AA131779, AA150020, AA150085, AA255834, AA548724, AA807007, AA825362, AA828253, N83830, N85321, N86360, AA205805, AA436905, AA709097, AA725018, Z22234, T03480, AI016816, AI093402, F08823, F10788
840748	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1610 of SEQ ID NO:500, b is an integer of 15 to 1624, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:500, and where b is greater than or equal to a + 14.	
840750	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 834 of SEQ ID NO:501, b is an integer of 15 to 848, where both a and b	

	correspond to the positions of nucleotide residues shown in SEQ ID NO:501, and where b is greater than or equal to a + 14.	
840751	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3178 of SEQ ID NO:502, b is an integer of 15 to 3192, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:502, and where b is greater than or equal to a + 14.	T39881, T40844, T40852, T40854, T40860, T40866, T50407, T50538, T55741, T94376, T94464, H27286, H81895, H94293, N78697, N99150, W19295, W21325, W24158, W25537, W45247, W72714, W93341, W95026, AA027063, AA065228, AA064926, AA070691, AA099952, AA127948, AA127982, AA142908, AA150910, AA460946, AA461252, AA230313, AA494344, AA534955, AA535709, AA557910, AA564147, AA564626, AA583542, AA523611, AA594463, AA595987, AA603874, AA613440, AA613660, AA635415, AA578985, AA568423, AA916523, AA922346, AA935323, AA650041, AA652730, AA654746, AA454065, AA486952, AA487075, AA487215, AA706108, AA722670, AA846544, AA853055, AA853056, AA853392, AA861048, AA991772, AI042420, AI074102, AI078712, AI041798, AI095622
840757	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 669 of SEQ ID NO:503, b is an integer of 15 to 683, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:503, and where b is greater than or equal to a + 14.	T50000, T50064, T50195, T58356, T58401, T58454, T59152, T94178, R06456, R06510, R72766, R72767, H02583, H02966, H04264, H39892, H41455, H44794, H46477, H46959, H51519, N45305, N54519, N54756, N63507, N64319, N76221, N94805, AA053467, AA056133, AA075160, AA078755, AA078756, AA079464, AA079463, AA079663, AA079767, AA088705, AA100045, AA100739, AA112276, AA112446, AA112416, AA113258, AA113355, AA113436, AA115702, AA115703, AA127146, AA132371, AA132616, AA147349, AA147400, AA151458, AA151459, AA156143, AA156398, AA157076, AA157164, AA157503, AA158148, AA158599, AA159018, AA159163, AA159790, AA159943, AA160779, AA160885, AA160895, AA160910, AA179280, AA181232, AA181237, AA181305, AA181255, AA181209, AA181326, AA182784, AA187267, AA187185, AA187224, AA187761, AA186497, AA186503, AA187019, AA187058, AA187039, AA187079, AA188443, AA192753, AA192829, AA192840, AA193199, AA193200, AA194570, AA421647, AA427634, AA469030, AA480763, AA482684, AA493670, AA501840, AA506094,

		AA507481, AA513173, AA514900, AA515423, AA524000, AA526363, AA526377, AA528558, AA528622, AA528762, AA533899, AA552652, AA555119, AA564174, AA564196, AA582614, AA583793, AA584240, AA588860, AA603073, AA604397, AA577162, AA662810, AA689248, AA689277, AA714332, AA714522, AA720655, AA729281, AA865192, AA888414, AA912488, AA934668, AA936157, AA947503, AA953047, AA961820, AA968484, AA976297, AA983436, AA988025, AA988424, AA991968, AA975722, AI074486, F19276, F19560, N84316, N85047, AA641348, AA641489, AA095374, AA095772, AA167520, AA652050, AA654250, F21094, F21095, AA434414, AA434512, AA470088, AA471285, AA486483, AA669755, AA431412, AA431815, AA434279, F22216, AA776904, AA835523, AA844771, AA845270, AA846028, AA846115, AA788715, AA861511, AA989575, AI027165, AI090099, D19841
840759	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2182 of SEQ ID NO:504, b is an integer of 15 to 2196, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:504, and where b is greater than or equal to a + 14.	R88018, N46360, N48866
840760	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 935 of SEQ ID NO:505, b is an integer of 15 to 949, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:505, and where b is greater than or equal to a + 14.	T73701, T73726, R09199, R09304, R18652, R48578, R48679, R73134, H72715, H97957, N56993, N73552, W74357, W76552, AA278851, AA508168, AA508735, AA512928, AA528091, AA766418, AA862669, AI003767, AI081289, AA417379, AA421192, AA609588, AA706851, AA285337, AA993015, AI001776, AI082525
840770	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 351 of SEQ ID NO:506, b is an integer of 15 to 365, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:506, and where b is greater than or equal to a + 14.	
840781	Preferably excluded from the present invention are one or more	T50486, T50620, T92253, T92297, T75117, R13719, R20099,

	polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2045 of SEQ ID NO:507, b is an integer of 15 to 2059, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:507, and where b is greater than or equal to a + 14.	R20756, R24896, R32452, R38544, R39672, R66654, R67375, R71953, R80144, R80145, H09238, H09239, H49089, H49178, H79086, H79087, H81170, H82251, H82354, H94594, H98533, H98540, H98561, N23328, N32489, N33553, N34608, N34615, N35704, N36791, N37062, N45951, N46374, N52614, N55340, N77346, N91916, W24093, W32300, W44887, W52202, W69110, W69235, W93030, W92919, AA010331, AA010332, AA070031, AA070335, AA075063, AA075062, AA085451, AA102617, AA113366, AA113445, AA133629, AA133675, AA131776, AA131809, AA136710, AA136808, AA151948, AA156555, AA157722, AA173681, AA181930, AA187541, AA187547, AA188217, AA186364, AA186932, AA459989, AA463983, AA464118, AA424144, AA424186, AA430453, AA216418, AA524319, AA535579, AA553797, AA582340, AA581875, AA586801, AA617881, AA579678, AA737057, AA736930, AA761601, AA807605, AA805212, AA809972, AA902407, AA902991, AA908502, AA916123, AA932301, AA947441, AA991523, N89110, N89294, C03132, AA093540, AA094654, AA149916, AA648245, AA447373, AA449202, AA598721, AA599096, AA670234, AA722507, AA779120, AA843601, AA844334, AA868803, AA906425, AA927243, AI021936, AI023003, AI022112, AI057609, AI073779, AI088646, AI093414, T17246, T16420, F01940, F02536, F03439, F05682, F06177, F06249, F04246, F07152, F07995
840789	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1323 of SEQ ID NO:508, b is an integer of 15 to 1337, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:508, and where b is greater than or equal to a + 14.	H23265, AA250917, AA789157, AI033562, Z38280, F08582
840790	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 717 of SEQ ID NO:509, b is an integer of 15 to 731, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID	H87973, H88155, N66473, AA143034, AA151105, AA528233, AA584398, AA864579

	NO:509, and where b is greater than or equal to a + 14.	
840791	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 930 of SEQ ID NO:510, b is an integer of 15 to 944, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:510, and where b is greater than or equal to a + 14.	H21100, H40810, R89801, AA563736, AA595316, AI056419
840798	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 503 of SEQ ID NO:511, b is an integer of 15 to 517, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:511, and where b is greater than or equal to a + 14.	AA206675, T18945
840802	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3637 of SEQ ID NO:512, b is an integer of 15 to 3651, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:512, and where b is greater than or equal to a + 14.	
840803	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1922 of SEQ ID NO:513, b is an integer of 15 to 1936, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:513, and where b is greater than or equal to a + 14.	T98263, R01276, R01777, H87694, N46514, AA064627, AA064791, AA076077, AA076159, AA083580, AA176354, AA186922, AA188542, AA192936, AA193132, AA234329, AA262890, AA284101, AA284046, AA827592, AA635005, AI015442, AI015761
840809	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1163 of SEQ ID NO:514, b is an integer of 15 to 1177, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:514, and where b is greater than or equal to a + 14.	
840811	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 918 of SEQ ID NO:515, b is an integer of 15 to 932, where both a and b	T60555

	correspond to the positions of nucleotide residues shown in SEQ ID NO:515, and where b is greater than or equal to a + 14.	
840813	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1145 of SEQ ID NO:516, b is an integer of 15 to 1159, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:516, and where b is greater than or equal to a + 14.	
840814	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2437 of SEQ ID NO:517, b is an integer of 15 to 2451, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:517, and where b is greater than or equal to a + 14.	T63362, T63686, T88888, T88889, T84250, T84251, R37080, R66483, H27722, H27723, R94403, H53971, H53972, H87801, H87857, N46002, N56932, W38961, W52373, AA032177, AA032176, AA034375, AA034374, AA042798, AA044611, AA044801, AA044666, AA056392, AA056506, AA085500, AA102623, AA100630, AA100629, AA122020, AA122019, AA127357, AA128179, AA126320, AA142870, AA150744, AA150871, AA169401, AA186750, AA188493, AA188849, AA189134, AA587050, AA740555, AA743649, AA805220, AA836673, AA837076, AA878369, AA906612, AA978334, AA977667, AA996072, AA640853, AA442873, C75140, AA628152, AA707458, AA725734, AA844284, AA868206, AA868822, AA884344, AA904845, AI082506, Z40412, F07337
840817	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 975 of SEQ ID NO:518, b is an integer of 15 to 989, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:518, and where b is greater than or equal to a + 14.	R24111, H13796, H39542, W87508, AA045018, AA055435, AA115239, AA137113, AA182593, AA459912, AA598757, AA772338, AI033925, AI041486, D31101
840825	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3301 of SEQ ID NO:519, b is an integer of 15 to 3315, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:519, and where b is greater than or equal to a + 14.	
840826	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the	R12213, T79259, R52573, H90609, N34140, AA007443, AA126085, AA203195, AA251452, AA613266, D81536, Z24821

	general formula of a-b, where a is any integer between 1 to 2347 of SEQ ID NO:520, b is an integer of 15 to 2361, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:520, and where b is greater than or equal to a + 14.	
840827	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2507 of SEQ ID NO:521, b is an integer of 15 to 2521, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:521, and where b is greater than or equal to a + 14.	
840828	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1289 of SEQ ID NO:522, b is an integer of 15 to 1303, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:522, and where b is greater than or equal to a + 14.	T86672, T86764, T87773, T87774, R35654, R35761, H57667, H58507, N80737, W07534, W81050, W80799, W95751, W95521, AA040152, AA040816, AA070448, AA213733, AA461551, AA460625, AA471038, AA592998, AA662015, AA747769, AA827708, AA830241, AA393711, AA400724, F21899, AI023732, AI033332, AI089332
840829	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1086 of SEQ ID NO:523, b is an integer of 15 to 1100, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:523, and where b is greater than or equal to a + 14.	T55234, T53974, AA121362, AA121372, F17737, AA614605, AA662456, AA832106, AA939005, AA454502, AA629986, AA928745, AA993303, AI017897, AI052396
840831	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1949 of SEQ ID NO:524, b is an integer of 15 to 1963, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:524, and where b is greater than or equal to a + 14.	
840836	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 780 of SEQ ID NO:525, b is an integer of 15 to 794, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:525, and where b is greater than or equal to a + 14.	R76181, N28426, AA249749, AA249759
840837	Preferably excluded from the present invention are one or more	T77944, R17636, H06632, W48792, W49617, AA121669,

	polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2585 of SEQ ID NO:526, b is an integer of 15 to 2599, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:526, and where b is greater than or equal to a + 14.	AA121741, AA876369, D80125, D79630, D79663, AA479160, AA773279, Z44214
840838	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1291 of SEQ ID NO:527, b is an integer of 15 to 1305, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:527, and where b is greater than or equal to a + 14.	T64743, R14614, H22783, H41174, H80646, H80683, N55490, N69823, N70603, N76977, AA036760, AA054012, AA057377, AA837761, AA987287, W04922, AA393640, AA435678, AA447554, AA448537, AA447593, AA448073, AA448092, AI080255, AI095479
840841	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1617 of SEQ ID NO:528, b is an integer of 15 to 1631, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:528, and where b is greater than or equal to a + 14.	R11201, R11254, R36000, R36374, R70779, R70831, R73839, R73838, R77816, R78184, H00444, H00487, H12294, H12343, H22227, H25152, H41334, H41582, H67783, H83813, N20077, N23800, N66638, N94763, W42581, W42593, AA029286, AA053585, AA053749, AA056556, AA058414, AA102286, AA112945, AA158256, AA160853, AA463315, AA464245, AA464353, AA426154, AA428022, AA554874, AA555227, AA594755, AA569425, AA572786, AA687312, AA721147, AA826769, AA907442, AA989227, AA436199, AA436324, AA723705, M91501, AA971764, AI057365, AI088555, AI090085, AI095652, AA772791
840842	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1930 of SEQ ID NO:529, b is an integer of 15 to 1944, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:529, and where b is greater than or equal to a + 14.	
840843	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1411 of SEQ ID NO:530, b is an integer of 15 to 1425, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:530, and where b is greater than or equal to a + 14.	R07636, R07683, R56490, H15484, H57022, H99251, N21556, N22947, N29473, N33077, N40267, N41499, N44647, N54167, N62284, N67127, N77575, N79824, W72340, W73971, AA035483, AA035015, AA099228, AA136670, AA136786, AA514951, AA558780, AA581821, AA767243, AA806856, AA832308, AA922693, D79892, N56078, C14941, AA654492, AA477457, AA477583, AA495757, AA495817, AA628697,

		AA628687, AA781710, AI004029, AI033065, AI076145, AI076166, AI080265, AI093765
840845	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1452 of SEQ ID NO:531, b is an integer of 15 to 1466, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:531, and where b is greater than or equal to a + 14.	H85970, H86679, N54585, N76666, W79488, W94055, AA012907, AA012992, AA018226, AA040388, AA040483, AA235697, AA424720, AA424881, AA468337, AA468480, AA470354, AA505886, AA533304, AA535176, AA558028, AA565018, AA568581, AA636065, AA569449, AA570195, AA580697, AA580574, AA769142, AA805257, AA857633, AA865266, AA974247, AA976018, AA983662, AI000909, AI074491, W94054, AA216680, AA283814, AA283815, AA293716, AA399618, AA411154, AA411153, AA430409, AA446547, AA446672, AA447405, AA447406, AA665639, Z19776, AA722802, AA776558, AA897739, AA773270, AI037944, AI056229, AI092063, Z39830, F02213, F04779, T65241, F12078, F09717
840847	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1644 of SEQ ID NO:532, b is an integer of 15 to 1658, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:532, and where b is greater than or equal to a + 14.	T93496, T96330, R33735, R56168, N29545, N47832, N52709, AA057861, AA057051, AA256421, AA423938, AA502373, AA594835, AA837984, AA937125, AA988563, AA642808, C16798, AA653712, D11569, D11567, D11568, D11572, AA759006
840851	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2843 of SEQ ID NO:533, b is an integer of 15 to 2857, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:533, and where b is greater than or equal to a + 14.	
840853	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1321 of SEQ ID NO:534, b is an integer of 15 to 1335, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:534, and where b is greater than or equal to a + 14.	T77874, T91147, T78073, T79015, H46575, H77369, N23303, N71319, N71370, W30700, W68080, W69637, AA029698, AA085548, AA100651, AA100446, AA150243, AA150317, AA179448, AA181464, AA187866, AA192778, AA257060, AA257151, AA483459, AA633204, AA579660, AA744468, AA745238, AA806004, AA806728, AA831848, AA832183, AA916113, AA916084, AA919159, AA918478, AI000093, AA094194, AA478126, AA488653, AA486512, AA598836,

		AA723044, AA844019, AA852336, AA904410, AA969896, AI002026, AA694486
840854	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2804 of SEQ ID NO:535, b is an integer of 15 to 2818, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:535, and where b is greater than or equal to a + 14.	
840858	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1383 of SEQ ID NO:536, b is an integer of 15 to 1397, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:536, and where b is greater than or equal to a + 14.	
840859	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1219 of SEQ ID NO:537, b is an integer of 15 to 1233, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:537, and where b is greater than or equal to a + 14.	T93690, AA046782, AA047471, H70453, W22335
840863	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1002 of SEQ ID NO:538, b is an integer of 15 to 1016, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:538, and where b is greater than or equal to a + 14.	
840868	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1665 of SEQ ID NO:539, b is an integer of 15 to 1679, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:539, and where b is greater than or equal to a + 14.	AA026007, AA053000, AA053532, AA078821, AA078789, AA126106, AA531460, AA553445, AA622619, AA877899, W63615, C03141, AA486740, C75022, AA682955, D25821
840869	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1066 of	

	SEQ ID NO:540, b is an integer of 15 to 1080, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:540, and where b is greater than or equal to a + 14.	
840870	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2245 of SEQ ID NO:541, b is an integer of 15 to 2259, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:541, and where b is greater than or equal to a + 14.	
840875	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1333 of SEQ ID NO:542, b is an integer of 15 to 1347, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:542, and where b is greater than or equal to a + 14.	N47871, N51132, N79772, W07271, W40335, AA659745, AA454850, AA455191, AA457737, AA480848
840876	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1887 of SEQ ID NO:543, b is an integer of 15 to 1901, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:543, and where b is greater than or equal to a + 14.	H40365, N30582, N57227, AA099212, AA143504, AA429979, AA489199, AA490948, AA503094, AA515940, AA515972, AA526974, AA565952, AA832525, AA847119, AA975937, C16546, AA205184, AA446121, AA446243, AA446429, AI093502, T25068
840881	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 828 of SEQ ID NO:544, b is an integer of 15 to 842, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:544, and where b is greater than or equal to a + 14.	N31249, N33927, N49638, AA169623, AA885642, AA885643, AA995981, D80629, AA654491
840883	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 764 of SEQ ID NO:545, b is an integer of 15 to 778, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:545, and where b is greater than or equal to a + 14.	
840886	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the	

	general formula of a-b, where a is any integer between 1 to 2128 of SEQ ID NO:546, b is an integer of 15 to 2142, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:546, and where b is greater than or equal to a + 14.	
840887	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1879 of SEQ ID NO:547, b is an integer of 15 to 1893, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:547, and where b is greater than or equal to a + 14.	
840891	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 616 of SEQ ID NO:548, b is an integer of 15 to 630, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:548, and where b is greater than or equal to a + 14.	AA011494, AA036641, AA040117, AA464582, AA229586, AA514441, AA557363, AA605134, AA632063, AA569111, AA731914, AA764872, AA834230, AA865217, AA865800, AA931605, AA975800, AA476216, AA477563, AA664440, AA906128, AA909907, AA994640, AI024748, AA701389
840892	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 572 of SEQ ID NO:549, b is an integer of 15 to 586, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:549, and where b is greater than or equal to a + 14.	T78188, H72434, H81179, N27050, N31296, N56740, N98857, W92285, AA010281, AA017504, AA018836, AA053984
840894	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1572 of SEQ ID NO:550, b is an integer of 15 to 1586, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:550, and where b is greater than or equal to a + 14.	R13791, R18500, R19446, R19717, R26638, R34992, R37650, R41499, R44273, R44694, R49667, R41499, R44273, R44694, R49667, H10866, H21080, H21081, H24215, H24216, H56529, H82728, H83602, H97231, H98771, N23492, N25150, N28896, N52055, N55071, N58330, N77279, N77697, N80782, N80789, W68363, W68498, AA035669, AA063521, AA099156, AA099254, AA100828, AA115528, AA115527, AA122370, AA121425, AA134022, AA131828, AA131994, AA151142, AA151141, AA150051, AA150036, AA197292, AA234967, AA234148, AA252624, AA419370, AA425774, AA426238, AA429953, AA244068, AA244221, AA291229, AA508903, AA521037, AA521047, AA558219, AA639444, AA730255, AA738405, AA764865, AA769630, AA808135, AA866207,

		AA875854, AA886233, AA911989, AA912330, AA918110, AA933817, AA960949, AA961737, AA970707, AA983973, AI084859, N87221, AA642352, C15736, AA095273, AA206988, AA649545, AA410978, AA443533, AA446839, AA599172, AA599632, AA625694, AA668705, AA678761, AA679282, AA843723, AI041402, AI041859, AI090256, Z40745, F03594, F03920, F07349, F07665, F07689, D12052, AA702844
840896	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2129 of SEQ ID NO:551, b is an integer of 15 to 2143, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:551, and where b is greater than or equal to a + 14.	T70566, T70837, R34229, R77683, H72423, N70430, W78960, W80454, AA157568, AA425171, AI081752, AA450124, AA450190, AA479929, AA626156, AI023982, AI079467, D20574
840897	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1620 of SEQ ID NO:552, b is an integer of 15 to 1634, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:552, and where b is greater than or equal to a + 14.	R08644, AA085919, AA085920, AA112589, AA291296, AA531553, AA534454, AA610556, AA632339, AA826535, AA873598, AA973899, AI000209, W22275, AA642711, AA285014, AA290836, AA291785, AA487868, AA487869, AA598896, AA732931, D20744
840898	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 264 of SEQ ID NO:553, b is an integer of 15 to 278, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:553, and where b is greater than or equal to a + 14.	
840904	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2644 of SEQ ID NO:554, b is an integer of 15 to 2658, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:554, and where b is greater than or equal to a + 14.	
840905	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1714 of SEQ ID NO:555, b is an integer of 15 to 1728, where both a and b	

	correspond to the positions of nucleotide residues shown in SEQ ID NO:555, and where b is greater than or equal to a + 14.	
840908	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3341 of SEQ ID NO:556, b is an integer of 15 to 3355, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:556, and where b is greater than or equal to a + 14.	
840909	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1065 of SEQ ID NO:557, b is an integer of 15 to 1079, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:557, and where b is greater than or equal to a + 14.	N26769, N30855, N91934, W17097, W76127, AA010929, AA011317, AA026824, AA026957, AA065084, AA064997, AA113980, AA113972, AA187311, AA187412, AA491244, AA503832, AA527886, AA603076, AA767201, AA768552, AA806008, AA857130, AA862053, W69334, N90880, AA285256, AA853981, AA971357, AI015443, AI037999, AI089498, F04542
840910	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 710 of SEQ ID NO:558, b is an integer of 15 to 724, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:558, and where b is greater than or equal to a + 14.	
840912	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3111 of SEQ ID NO:559, b is an integer of 15 to 3125, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:559, and where b is greater than or equal to a + 14.	T89929, T97560, T97607, T98767, T98768, R75684, R76638, H29662, R91419, H63674, H84562, N22625, N23668, N59616, N67124, N75308, N78169, W04760, W15411, W15522, W31605, W39524, AA007425, AA007426, AA044991, AA044990, AA161382, AA161383, AA190884, AA190852, AA195140, AA195346, AA195347, AA278498, AA515881, AA523692, AA557400, AA579985, AA732611, AA813932, AI053747, D80095, D80559, D80940, D82547, D82557, D82494, C01801, R29401, AA404683, AA404214, AA634226, AA456641, AA812584, AA884056, AI004948, AI033808, AI038706, AI073466, D20935, Z40790, Z45057, F02232, F05993, AA700153, AA700480
840916	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2631 of	

	SEQ ID NO:560, b is an integer of 15 to 2645, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:560, and where b is greater than or equal to a + 14.	
840917	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1703 of SEQ ID NO:561, b is an integer of 15 to 1717, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:561, and where b is greater than or equal to a + 14.	H30515, H58512, AA428216, AA429793, AA888482, AA402294, AA478415, AA665865, AI079558
840918	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2403 of SEQ ID NO:562, b is an integer of 15 to 2417, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:562, and where b is greater than or equal to a + 14.	T63366, T63794, T63819, T72173, T72951, T74098, T74471, R40321, R54813, R40321, H28292, H87420, H96805, H99895, H99896, N21575, N26498, N35550, N35899, N43971, N46316, N50289, N62230, N67269, N67736, N79322, W03582, W20379, W35114, W93987, W93993, W93961, AA002131, AA002085, AA010861, AA010895, AA032150, AA039874, AA046207, AA046213, AA075922, AA076246, AA076245, AA082698, AA100666, AA100665, AA102690, AA101322, AA115198, AA115199, AA127068, AA125791, AA130142, AA130164, AA160133, AA160152, AA181132, AA223399, AA223717, AA223794, AA225618, AA225617, AA225893, AA226087, AA281188, AA467866, AA532633, AA548553, AA548715, AA565709, AA595388, AA604287, AA610139, AA574387, AA574403, AA576771, AA827594, AA857936, AA862174, AA886789, AA894576, AA933053, AA961640, AA962084, AA971648, AI017658, AI089036, U48642, AI084032, W29098, AA041518, AA206338, AA206730, AA204730, AA218606, AA285284, AA293327, D11555, AA450117, AA626655, AA666366, AA679791, AA844183, AA883770, AA904568, AA904956, AA913275, AA913772, Z39779, F06739, F07232
840922	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1530 of SEQ ID NO:563, b is an integer of 15 to 1544, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:563, and where b is greater than or equal to a + 14.	

840923	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2285 of SEQ ID NO:564, b is an integer of 15 to 2299, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:564, and where b is greater than or equal to a + 14.	
840927	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 350 of SEQ ID NO:565, b is an integer of 15 to 364, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:565, and where b is greater than or equal to a + 14.	
840928	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2467 of SEQ ID NO:566, b is an integer of 15 to 2481, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:566, and where b is greater than or equal to a + 14.	R52991, R52992, AA075795, AA236859, AA237058, AA258294, AA490530, AA582199, AA594981, AA768625, AA918784, AA400122, AA400211, AA599540, AA620310, AA757241, AA853706, Z44647
840929	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1350 of SEQ ID NO:567, b is an integer of 15 to 1364, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:567, and where b is greater than or equal to a + 14.	T65391, T65468, T82268, T83555, R23120, R23121, H05767, H15242, H15243, N27484, N75846, W07429, W55965, W55966, W69486, W69610, AA024480, AA024481, AA035363, AA035364, AA036732, AA045784, AA045785, AA054537, AA054576, AA058867, AA081962, AA082833, AA122107, AA122108, AA160026, AA506569, AA582633, AA593717, AA593757, AA596048, AA741487, AA830268, AA834091, AA917654, AA922770, AA948018, C00527, AA648362, AA448872, AA447937, AA708846, AA769947, AA775569, AA835167, AI090227, F02032, F11824, F09473
840930	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1592 of SEQ ID NO:568, b is an integer of 15 to 1606, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:568, and where b is greater than or equal to a + 14.	T66390, R13067, R20192, R40498, R44978, R54122, R40498, R44978, R55825, R55910, R56182, H05938, H10239, H13040, H22780, H22987, H26826, H28018, R84898, R85844, N48284, N49013, W59970, AA029938, AA030050, AA037606, AA040869, AA043138, AA147575, AA152015, AA152022, AA152089, AA152096, AA150150, AA152219, AA156446, AA429964, AA470402, AA528114, AA594982, AA595134, AA886444,

		AA972352, F18878, C04576, AA090702, C16326, AA649510, AA211287, AA211332, AA443358, AA446384, AA666350, AA993887, AI032649, AI096674, Z24984, Z25108, Z25360, Z33590, T25134, Z37011, F12229, F00286, F09858
840931	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1371 of SEQ ID NO:569, b is an integer of 15 to 1385, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:569, and where b is greater than or equal to a + 14.	AA164298, AA164299, AA215696, AA553729, AA600053
840941	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1130 of SEQ ID NO:570, b is an integer of 15 to 1144, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:570, and where b is greater than or equal to a + 14.	T71972, T72113, N66952, AA037833, AA037834, AA503937, AA514259, AA568671, C04493, AA400259, AA703387, AA897154, AA905309, AA991791, AI091736, AI097161, AA699338, AA699546
840944	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2740 of SEQ ID NO:571, b is an integer of 15 to 2754, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:571, and where b is greater than or equal to a + 14.	R53077, R53166, N66228, N66588, N98299, N98791, W52420, W58722, AA054166, AA102647, AA101300, AA224382, AA224448, AA504618, AA504713, AA505965, AA577583, AA766244, AA837194, AA936390, AA938580, AA969268, AI056953, Z25291, Z28894, T25120
840945	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2643 of SEQ ID NO:572, b is an integer of 15 to 2657, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:572, and where b is greater than or equal to a + 14.	
840948	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2338 of SEQ ID NO:573, b is an integer of 15 to 2352, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:573, and where b is greater than or equal to a + 14.	
840949	Preferably excluded from the present invention are one or more	

	polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 314 of SEQ ID NO:574, b is an integer of 15 to 328, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:574, and where b is greater than or equal to a + 14.	
840953	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1664 of SEQ ID NO:575, b is an integer of 15 to 1678, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:575, and where b is greater than or equal to a + 14.	
840954	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2494 of SEQ ID NO:576, b is an integer of 15 to 2508, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:576, and where b is greater than or equal to a + 14.	T70122, R01105, R01854, R26511, R50976, W39281, W88823, AA190914, AA220964, AA223912, AA224067, AA292591, AA516293, AA888082, AA093864, AA644303, AA668429, AA680062, AA705885, Z25045, Z25169, Z28742, Z40110, F06996, F00269
840958	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1517 of SEQ ID NO:577, b is an integer of 15 to 1531, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:577, and where b is greater than or equal to a + 14.	T92026, T92127, T96602, T99639, R07023, R70248, R74432, H24617, H25443, H25488, H25814, H39512, H49218, H49404, H85371, H98480, N21621, N28860, N32291, N44577, N93796, W19136, W46407, N89924, AA252381, AA252643, AA230168, AA251928, AA252509, AA280831, AA281028, AA570114, AA570316, AA688054, AA731686, AA731363, AA737178, AA743784, AA761782, AA805326, AA806145, AA806698, AA807626, AA810694, AA811702, AA857654, AA903433, AA947731, AA976482, AA977020, D80646, AA448459, AA722871, AA834947, AA844661, AA868828, AA912953, AA971589, AI032540, AI093489, Z33450
840960	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1230 of SEQ ID NO:578, b is an integer of 15 to 1244, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:578, and where b is greater than or equal to a + 14.	R80950, R81055, H17096, H17714, H21600, H28031, H39514, N25283, N48074, N93030, N93491, AA005164, AA005250, AA037756, AA039247, AA062857, AA062864, AA159264, AA461323, AA482290, AA523938, AA548271, AA602298, AA612800, AA580232, AA878960, AA954638, AA983694, AA948176, AA452852, AA452868, AA628205, AA629208, AA707757, AA884020, AI086383, AI092362, AA952907,

		F03951, F04326, F07686
840968	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2511 of SEQ ID NO:579, b is an integer of 15 to 2525, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:579, and where b is greater than or equal to a + 14.	
840969	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3992 of SEQ ID NO:580, b is an integer of 15 to 4006, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:580, and where b is greater than or equal to a + 14.	
840972	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 551 of SEQ ID NO:581, b is an integer of 15 to 565, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:581, and where b is greater than or equal to a + 14.	
840973	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2514 of SEQ ID NO:582, b is an integer of 15 to 2528, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:582, and where b is greater than or equal to a + 14.	T92934, T93051, T95827, T95922, R01416, R01417, R14186, R40475, R40475, R62217, H02303, H02413, N91928, N92794, W19380, W24105, W24106, W92317, W92353, AA009695, AA009414, AA016232, AA022718, AA022810, AA031668, AA031669, AA135522, AA135584, AA233766, AA233817, AA468889, AA502015, AA514448, AA524548, AA613782, AA740659, AA831839, AA856642, AA865523, AA933090, AA937529, AA937525, AA995177, D45313, D80956, C04688, AA642850, C15075, C15074, AA652169, AA404513, AA485401, AA485562, AA626502, AA703641, AI014270, AI027694, AI052552, AI080105, AI094104, Z24781, Z28475, D20204, AA699913
840975	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 493 of SEQ ID NO:583, b is an integer of 15 to 507, where both a and b	AA187971, AA491557

	correspond to the positions of nucleotide residues shown in SEQ ID NO:583, and where b is greater than or equal to a + 14.	
840978	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1917 of SEQ ID NO:584, b is an integer of 15 to 1931, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:584, and where b is greater than or equal to a + 14.	
840980	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1006 of SEQ ID NO:585, b is an integer of 15 to 1020, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:585, and where b is greater than or equal to a + 14.	T91979, T85031, R51511, H08105, H14962, H84344, H95886, N67113, AA001485, AA033681, AA045053, AA045054, AA460816, AA548181, AA602217, AA627119, AA919072, N85463, AA090718, AA090747, AA205839, AA215860, AA889349, AI005058, AI051749
840982	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 753 of SEQ ID NO:586, b is an integer of 15 to 767, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:586, and where b is greater than or equal to a + 14.	
840985	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 833 of SEQ ID NO:587, b is an integer of 15 to 847, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:587, and where b is greater than or equal to a + 14.	AA469388, AA469387, AA579307, AA838301
840989	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2144 of SEQ ID NO:588, b is an integer of 15 to 2158, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:588, and where b is greater than or equal to a + 14.	T56570, T56419, T74072, H02553, H02636, H05217, H28221, H28270, H53671, N24892, N26327, N36312, N39771, N43761, W19923, N91268, AA132017, AA132120, AA195204, AA195313, AA196452, AA196696, AA227654, AA232501, AA232165, AA429770, AA281620, AA281676, AA468179, AA515887, AA533678, AA551958, AA639446, AA577363, AA579740, AA721360, AA729621, AA769527, AA814423, AA826344, AA903583, D81898, D81970, C04597, AA216528, AA216535, AA442781, AA452285, AA452436, AA709278, AA718938,

		AA771705, AA771724, AA868151, AA993850, AI033921, Z32830, AA952909, F11180, F11002, F11632
840991	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2285 of SEQ ID NO:589, b is an integer of 15 to 2299, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:589, and where b is greater than or equal to a + 14.	T81125, N29118, N36444, N46478, AA169588, AA169707, AA190390, AA197190, AA465591, AA569663, AA572882, AA927990, AI031844, W26259, W26429, W27367, W27994, W28877, AA453067, Z39013, Z42882
840996	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2166 of SEQ ID NO:590, b is an integer of 15 to 2180, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:590, and where b is greater than or equal to a + 14.	R11816, T80577, R18182, R55973, R59293, R61044, H08547, H08548, H16428, AA001999, AA001722, AA181466, AA181638, AA530935, AA811299, AA774853, AA853584, T48535
840997	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1179 of SEQ ID NO:591, b is an integer of 15 to 1193, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:591, and where b is greater than or equal to a + 14.	H81891, N27695, AA242758, AA242898, AA262282, AA463638, AA443047, AA677853
840998	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1988 of SEQ ID NO:592, b is an integer of 15 to 2002, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:592, and where b is greater than or equal to a + 14.	H39956, R95173, N21653, N59206, AA126765, W25859, AA126814, AA411155, AA479348, AA663608, AA723137, AA904646, AA936314
840999	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1000 of SEQ ID NO:593, b is an integer of 15 to 1014, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:593, and where b is greater than or equal to a + 14.	T59001, R38613, AA558946, D80113, AA628765, AA931368, AI087859, AI087860, AI088020, AI088042, AI088041, Z41502, T59074, F10347
841000	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 319 of	T63281

	SEQ ID NO:594, b is an integer of 15 to 333, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:594, and where b is greater than or equal to a + 14.	
841002	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1106 of SEQ ID NO:595, b is an integer of 15 to 1120, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:595, and where b is greater than or equal to a + 14.	N75236, N79007, W33128, AA044565, AA192107, AA194732, AA430142, AA602405, AA732494, AA730246, AA767992, AA836339, AI083657, AA206755, AA205076, AA649037, AA446467, AA722661, AA993269, AA994380, AI005394, AI032012
841003	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 518 of SEQ ID NO:596, b is an integer of 15 to 532, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:596, and where b is greater than or equal to a + 14.	N50091, W78173, W79236, AA758361, AA992853
841008	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1480 of SEQ ID NO:597, b is an integer of 15 to 1494, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:597, and where b is greater than or equal to a + 14.	T71281, T71345, T77436, R08136, R08137, R20906, R21385, R22903, R39269, R43069, R46481, R51904, R52702, R43069, R46481, R43120, R79482, H13227, H18911, H19203, H65049, H65050, H94075, H96326, H96721, N21076, N21154, N21166, N23977, N34347, N42814, N73453, N93204, W02856, W20197, W38726, W38956, W56890, N90551, AA007554, AA037417, AA040911, AA116130, AA116131, AA169544, AA169728, AA169445, AA173030, AA210740, AA211832, AA211833, AA420515, AA420563, AA420747, AA420808, AA459156, AA469336, AA480571, AA548615, AA554507, AA554716, AA559111, AA594680, AA602634, AA568997, AA857653, AA938636, AA962481, AA969819, AA988963, C01221, N87866, N88166, C06426, C16205, C16225, C16262, C16328, C16346, C16567, AA093646, AA094628, AA215845, AA248299, AA450084, AA450101, AA450141, AA450164, AA452926, AA453098, AA677261, AA704706, AA776452, AA782448, AA905622, AI024304, AI027088, T10244, T24104, F10814
841013	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2174 of	

	SEQ ID NO:598, b is an integer of 15 to 2188, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:598, and where b is greater than or equal to a + 14.	
841014	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1259 of SEQ ID NO:599, b is an integer of 15 to 1273, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:599, and where b is greater than or equal to a + 14.	R13850, R36993, R40384, R49290, R49290, R70449, H20581, H22501, H41342, W52797, W63724, AA026917, AA149462, AA223955, AA232557, AA416604, AA282009, AA284187, AA534348, N83640, W28199, AA641025, AA652459, AA707275, D19833
841015	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1225 of SEQ ID NO:600, b is an integer of 15 to 1239, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:600, and where b is greater than or equal to a + 14.	T60712, T39204, T40475, T89115, R23975, R42835, R50864, R42835, R80780, R80929, R80980, R81030, R81287, H45854, R85410, H85126, H85165, H86110, H92458, H92459, H96689, N45682, N48966, N64273, N67340, W38863, W60856, W73806, W79809, W79590, AA031812, AA031892, AA039603, AA056740, AA058411, AA069773, AA069809, AA127774, AA133361, AA150512, AA186437, AA188784, AA215296, AA236042, AA250827, AA250884, AA258206, AA459963, AA480598, AA484831, AA524510, AA554692, AA627856, AA633499, AA633500, AA573552, AA577009, AA661865, AA838393, AA838126, AA872284, AA888617, AA954248, AA972651, AA974294, AA978242, AI000986, N84928, W28888, AA093374, AA095419, AA649576, AA447092, AA628724, AA635022, AA635099, AA708921, AA782622, AA845435, AA852359, AA283454, AA860493, AA905955, AI015482, AI033996, AI057611, AI041421, AI097090, T15984, F04083, F04704, AA693482
841018	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1272 of SEQ ID NO:601, b is an integer of 15 to 1286, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:601, and where b is greater than or equal to a + 14.	
841019	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 390 of	AA248515

	SEQ ID NO:602, b is an integer of 15 to 404, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:602, and where b is greater than or equal to a + 14.	
841024	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1154 of SEQ ID NO:603, b is an integer of 15 to 1168, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:603, and where b is greater than or equal to a + 14.	
841025	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 444 of SEQ ID NO:604, b is an integer of 15 to 458, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:604, and where b is greater than or equal to a + 14.	AA188466
841026	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 897 of SEQ ID NO:605, b is an integer of 15 to 911, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:605, and where b is greater than or equal to a + 14.	N72911, AA148215, AA166925, AA228038, AA228148, AA483775, AA504475, AA740596, AA742681, AA808693, AA811844, AI054163, D12456, D12055, AA446237, AA599068, AI075720
841027	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 724 of SEQ ID NO:606, b is an integer of 15 to 738, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:606, and where b is greater than or equal to a + 14.	H41598, H62017, H69575, H69596, H84745, H95065, N36218, N54430, N80053, W52484, AA010201, AA235462, AA513394, AA559062, H84833, AA574343, AA835915, AA872643, AA877236
841029	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1334 of SEQ ID NO:607, b is an integer of 15 to 1348, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:607, and where b is greater than or equal to a + 14.	T50950, T40351, T41210, T64654, T99782, T99883, R12658, R20557, R48599, R48701, R20557, H10512, R82975, R83815, H51313, H51908, H54291, H54369, H57072, H57073, H70169, H81838, H89935, H91980, N26532, N26640, N35643, N39712, N39735, N44132, N45472, N46821, N66762, N68174, N73964, N80633, N93213, N93218, N94936, W19558, W19581, W20315, W33192, W37258, W38673, W38998, W38807, W39086, W44806, W49655, W49729, W52842, W56034, W56019,

		W72523, W96449, W96546, N90712, AA022694, AA022787, AA033992, AA033993, AA055233, AA128163, AA125976, AA151620, AA228010, AA234230, AA235616, AA460804, AA428125, AA428126, AA244254, AA244044, AA282782, AA459422, AA465647, AA514260, AA524819, AA526652, AA527010, AA557557, AA593780, AA594299, AA604168, AA612788, AA622842, AA639066, AA729180, AA730491, AA737387, AA814201, AA847016, AA872392, AA873523, AA885963, AA902850, AA946931, AA968795, AA974320, AA977816, AI094935, AA642338, AA093758, AA094834, AA650022, AA248350, AA402422, AA446745, AA449102, AA449538, AA482267, AA431490, AA431697, AA432060, AA706083, AA706225, AA723554, AA724604, AA732823, AA772101, AA772330, AA781604, AA782387, AA843140, AA843480, AA843756, AA846144, AA846155, AA845500, AA854399, AA855096, AA860829, AA888776, AA889009, AI023231, AI028453, AI031906, AI031928, AI038365, AI051907, AI050990, AI056013, AI066647, AI073764, AI074709, AI076720, AI077283, AI040402, AI087021, AI088075, AI087912, AI092000, AI091592, AI092431, AI092579, AI095442, D20747, F05340, AA694556
841030	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 708 of SEQ ID NO:608, b is an integer of 15 to 722, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:608, and where b is greater than or equal to a + 14.	T85016
841031	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 316 of SEQ ID NO:609, b is an integer of 15 to 330, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:609, and where b is greater than or equal to a + 14.	
841034	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the	

	general formula of a-b, where a is any integer between 1 to 1852 of SEQ ID NO:610, b is an integer of 15 to 1866, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:610, and where b is greater than or equal to a + 14.	
841036	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2162 of SEQ ID NO:611, b is an integer of 15 to 2176, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:611, and where b is greater than or equal to a + 14.	
841039	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3605 of SEQ ID NO:612, b is an integer of 15 to 3619, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:612, and where b is greater than or equal to a + 14.	
841040	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1413 of SEQ ID NO:613, b is an integer of 15 to 1427, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:613, and where b is greater than or equal to a + 14.	
841048	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1419 of SEQ ID NO:614, b is an integer of 15 to 1433, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:614, and where b is greater than or equal to a + 14.	N69349, W37995, W37996, AA099842, AA129834, AA134879, AA136131, AA136101, AA213847, AA278288, AA278834, AA639630, AA743611, AA745858, AA765478, AA829501, AA830648, AA837909, AA877341, AA887480, AA910616, C01321, AA134878, AA410913, AA441809, AA441871, AA447551, AA679476, F13794
841049	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 492 of SEQ ID NO:615, b is an integer of 15 to 506, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:615, and where b is greater than or equal to a + 14.	AA206670
841050	Preferably excluded from the present invention are one or more	R13856, R36998, H88745, H88749, H88750, H88744, H88745,

	polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2160 of SEQ ID NO:616, b is an integer of 15 to 2174, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:616, and where b is greater than or equal to a + 14.	H88750, N20597, N27562, N28993, N40383, W23671, W42418, W42515, AA017276, AA054535, AA054527, AA081056, AA083641, AA165258, AA165257, AA195316, AA195497, AA504774, AA731655, AA743407, AA827654, AI074376, AA096064, AA677874, AI049801, T10385, D31353, AA700430
841052	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3133 of SEQ ID NO:617, b is an integer of 15 to 3147, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:617, and where b is greater than or equal to a + 14.	
841054	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2515 of SEQ ID NO:618, b is an integer of 15 to 2529, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:618, and where b is greater than or equal to a + 14.	
841055	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 537 of SEQ ID NO:619, b is an integer of 15 to 551, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:619, and where b is greater than or equal to a + 14.	T86070
841056	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1721 of SEQ ID NO:620, b is an integer of 15 to 1735, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:620, and where b is greater than or equal to a + 14.	T65020, T66102, T74444, R12529, R36487, R36488, R37425, R52082, R52176, N58833, N75250, AA573305, AA687450, AA687507, AA810182, AA815088, AA908253, AI084103, AA489756, AA844081, AA844438, AA854762, AA897722, F11861, F12468, T83267, F09506, F10088
841060	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1012 of SEQ ID NO:621, b is an integer of 15 to 1026, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:621, and where b is greater than or equal to a + 14.	

841061	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 656 of SEQ ID NO:622, b is an integer of 15 to 670, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:622, and where b is greater than or equal to a + 14.	W47450, AA491124
841062	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2149 of SEQ ID NO:623, b is an integer of 15 to 2163, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:623, and where b is greater than or equal to a + 14.	
841063	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 587 of SEQ ID NO:624, b is an integer of 15 to 601, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:624, and where b is greater than or equal to a + 14.	AA227288, AA282718
841067	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 579 of SEQ ID NO:625, b is an integer of 15 to 593, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:625, and where b is greater than or equal to a + 14.	
841074	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2258 of SEQ ID NO:626, b is an integer of 15 to 2272, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:626, and where b is greater than or equal to a + 14.	T39947, T40903, T90518, T90617, T86882, T86883, R11373, T79972, T83358, T83504, R16291, R18540, R18728, R21852, R21872, R32969, R33513, R34056, R35153, R37578, R41528, R42089, R50812, R41528, R42089, R63072, R63114, R66886, R68286, R68328, R77261, R77305, H04160, H04159, H09820, H09915, H11374, H11399, H11475, H11580, H20564, H20656, H20724, H20725, H45913, R87571, H71492, H71493, H77970, H77971, H85921, H95617, H97011, H97137, H97973, H99201, H99869, N20626, N21042, N23341, N23509, N27621, N27863, N28554, N28813, N33434, N35711, N36525, N40636, N42409, N50418, N50473, N55217, N55526, N77009, W15345, W31916,

		W39297, W39437, W40562, W40586, W52515, W56373, W56584, W56673, W56738, W60072, W73328, AA001060, AA001061, AA001355, AA012936, AA013022, AA020854, AA021013, AA021245, AA021350, AA041249, AA044791, AA057517, AA070118, AA081114, AA081289, AA081518, AA081758, AA081654, AA081910, AA081807, AA083386, AA083520, AA084143, AA084169, AA084637, AA102204, AA101101, AA112305, AA112273, AA113158, AA113205, AA113234, AA113290, AA112514, AA114269, AA114292, AA121997, AA121998, AA122357, AA122358, AA127073, AA125796, AA134357, AA134635, AA148203, AA148204, AA148658, AA148659, AA156277, AA156388, AA158662, AA159027, AA160336, AA159855, AA160818, AA176261, AA176262, AA181259, AA182937, AA187516, AA186906, AA186943, AA210754, AA211829, AA223289, AA223297, AA223271, AA223898, AA223866, AA223865, AA223930, AA224002, AA226834, AA227007, AA251494, AA464562, AA464663, AA282038, AA282381, AA282799, AA282890, AA454945, AA455324, AA459366, AA459591, AA471068, AA493188, AA506956, AA515184, AA525415, AA528016, AA531574, AA557548, AA559080, AA558794, AA601508, AA602820, AA604093, AA580330, AA665041, AA688154, AA714131, AA721076, AA729400, AA730738, AA736940, AA745800, AA746251, AA747771, AA749097, AA761791, AA765245, AA769486, AA810468, AA809803, AA815070, AA815124, AA825529, AA827628, AA827818, AA830566, AA831651, AA832026, AA836109, AA856618, AA858034, AA862500, AA908700, AA916911, AA923104, AA911251, AA922814, AA948643, AA975963, AA976127, AA988496, AA995369, AI015981, D82125, N85599, N85825, W60998, N87121, N88156, C05715, C05853, AA046846, AA641779, AA070117, C20828, C21327, AA159483, AA206049, AA206104, AA206105, AA206439, AA206436, AA206529, AA206577, AA206641, AA205227, AA205214, AA205483, AA205488, AA205554, AA205495, AA205683, AA205707, AA205655, AA648896, AA649019, AA211090, AA211201, AA219240,

		AA219379, AA248392, AA263057, AA436015, AA436120, AA444131, AA449168, AA485456, AA488660, C74998, C75053, C75178, C75578, C75650, AA598408, AA600229, AA633997, AA664255, AA670477, AA456958, AA457067, AA457333, AA707431, AA708046, AA708052, AA722286, AA679711, AA774733, AA776895, AA778320, AA782343, AA852970, AA852969, AA853367, AA854017, AA884081, AA913264, AI003524, AI003161, AI061383, AI079587, AI080214, AI085729, AI088540, AI088599, T10660, T11369, T16057, T17106, Z41696, T16213, T27465, F01519, F02134, T54069, F07296, F13614, F13652, AA702026
841076	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 857 of SEQ ID NO:627, b is an integer of 15 to 871, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:627, and where b is greater than or equal to a + 14.	
841081	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 765 of SEQ ID NO:628, b is an integer of 15 to 779, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:628, and where b is greater than or equal to a + 14.	H80595, N66964, W60868, W60944, AA554024, AA581858, AA603775, AA569390, AA721420, AA730838, AA746990, AA764955, AA824533, AA886662, AA902151, AA922977, AA931633, AI004155, C17761, AA643235, AA249456, AA401851, AA447213, AA769929, AA861067, AA868853, AI001993, AI038228, AI080577, D12310, AA699302, AA700733
841083	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1821 of SEQ ID NO:629, b is an integer of 15 to 1835, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:629, and where b is greater than or equal to a + 14.	
841089	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1083 of SEQ ID NO:630, b is an integer of 15 to 1097, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:630, and where b is greater than or equal to a + 14.	T97583, H27459, H28283, H30123, H30163, H40493, H64399, H99038, N20188, N29090, W24593, W47194, W47309, W51990, W52638, W56428, W56312, W73795, W78984, W80386, W85832, W87763, W87679, W93594, W93490, AA010192, AA010091, AA229878, AA230283, AA508851, AA553908, H64447, AA582764, AA805299, AA877051, AI053512,

		AI053734, AI054001, AI054092, AI054119, AI054274, AI054309, AA758790, AA972288, AI028150, AI077801, AI092052, D20235, T97631
841093	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1523 of SEQ ID NO:631, b is an integer of 15 to 1537, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:631, and where b is greater than or equal to a + 14.	
841097	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1887 of SEQ ID NO:632, b is an integer of 15 to 1901, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:632, and where b is greater than or equal to a + 14.	
841098	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1736 of SEQ ID NO:633, b is an integer of 15 to 1750, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:633, and where b is greater than or equal to a + 14.	T39572, R32405, R78435, R82780, H01823, W23901, AA705025
841101	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1912 of SEQ ID NO:634, b is an integer of 15 to 1926, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:634, and where b is greater than or equal to a + 14.	R11755, R12465, R23435, R54254, H10274, N31847, W63594, AA488942, AA581018, AA767423, N56490, W26165, N87429, AA093862, Z41898
841113	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1332 of SEQ ID NO:635, b is an integer of 15 to 1346, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:635, and where b is greater than or equal to a + 14.	
841115	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the	

	general formula of a-b, where a is any integer between 1 to 1570 of SEQ ID NO:636, b is an integer of 15 to 1584, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:636, and where b is greater than or equal to a + 14.	
841116	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1649 of SEQ ID NO:637, b is an integer of 15 to 1663, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:637, and where b is greater than or equal to a + 14.	
841117	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3933 of SEQ ID NO:638, b is an integer of 15 to 3947, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:638, and where b is greater than or equal to a + 14.	
841125	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1413 of SEQ ID NO:639, b is an integer of 15 to 1427, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:639, and where b is greater than or equal to a + 14.	R40268, R40268, R60037, H05829, H71311, H71355, H94227, N30711, N56686, W70033, W80987, W94564, W92648, AA036715, AA043642, AA045098, AA045127, AA057355, AA070703, AA150080, AA186980, AA196549, AA513466, AA564458, H92998, AA584288, AA587915, AA746344, AA749431, AA836837, AA946608, AA977318, AI000432, AI000474, AA150015, AA487107, AA777153, AA778651, AA778720, AA824341, AI038357, AI038499, AI076148, AI077415, AI040155, AI090830, T16464, AA682387
841127	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 906 of SEQ ID NO:640, b is an integer of 15 to 920, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:640, and where b is greater than or equal to a + 14.	N56381
841128	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1692 of SEQ ID NO:641, b is an integer of 15 to 1706, where both a and b	

	correspond to the positions of nucleotide residues shown in SEQ ID NO:641, and where b is greater than or equal to a + 14.	
841132	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2156 of SEQ ID NO:642, b is an integer of 15 to 2170, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:642, and where b is greater than or equal to a + 14.	
841133	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1698 of SEQ ID NO:643, b is an integer of 15 to 1712, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:643, and where b is greater than or equal to a + 14.	
841134	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1779 of SEQ ID NO:644, b is an integer of 15 to 1793, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:644, and where b is greater than or equal to a + 14.	T74160, R06227, R06228, R20261, N39674, AA010503, AA010502, AA258312, AA258463, AA261908, AA737428, AA775864, F12625
841135	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2665 of SEQ ID NO:645, b is an integer of 15 to 2679, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:645, and where b is greater than or equal to a + 14.	T87474, T81011, T98855, T99451, R12662, R20561, R35774, R20561, H21581, H30226, H30799, H38312, R87419, R87929, H60442, H60488, H82962, H83193, N66578, N98838, W02116, W32577, W74585, W94377, AA228054, AA228143, AA242795, AA252182, AA482136, AA491273, AA503197, AA603089, AA740514, AA847687, AA872051, AA904292, AA908878, AA937801, AA937818, AA937819, AA989229, AI081549, W27606, W28260, C01173, AA090299, AA292408, AA394244, AA430326, AA443626, AA678857, AA779761, AA838766, AA860401, AA890101, AA772701, AA905819, AA913578, AA913854, AA916557, AI073446, AI040348, AI086394, F04810, F08603
841136	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 818 of	T75313, R38678, H08805, H08881, H29671, W45345, AA460481, AA461049, AA514387, AA928902, C06109, C15637, AI033621, F13191, F10796

	SEQ ID NO:646, b is an integer of 15 to 832, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:646, and where b is greater than or equal to a + 14.	
841138	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1311 of SEQ ID NO:647, b is an integer of 15 to 1325, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:647, and where b is greater than or equal to a + 14.	T74162, R08056, R37869, R51362, H95451, N47377, N50420, N51509, N56992, N63081, W02768, W74061, W78768, W81120, AA004354, AA004355, AA010410, AA011238, AA194618, AA461179, AA492472, AA602060, AA742194, AA886331, AA904165, AA947316, AA969817, C02127, AA642584, AA393447, AA398743, AA449962, AA706890, AA757113, AA777532, AA812606, AA971808, AA947589, AI033060, AI077473, F12626, F10242
841139	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 592 of SEQ ID NO:648, b is an integer of 15 to 606, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:648, and where b is greater than or equal to a + 14.	
841141	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1682 of SEQ ID NO:649, b is an integer of 15 to 1696, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:649, and where b is greater than or equal to a + 14.	T70178, T78370, H06915, H19407, H20353, H59580, H68320, AA282429, AA504514, AA504598, AA564110, AA622709, AA635277, AA814782, AA094950, AA890363, AI082674, T69852
841142	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3045 of SEQ ID NO:650, b is an integer of 15 to 3059, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:650, and where b is greater than or equal to a + 14.	R16159, R55052, R59723, R59832, R72647, R72726, H60244, N33957, N49667, N73245, N79519, N79654, W16510, W16960, AA032239, AA033647, AA463305, AA280166, AA729292, AA954720, AA988492, AI015581, C02527, AA393868, AA478565, AA478698, AA773346, AI032816, AI078056, Z38500, Z42263, R15417, AA701338
841145	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1352 of SEQ ID NO:651, b is an integer of 15 to 1366, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:651, and where b is greater than or equal to a + 14.	T50010, R23613, R26166, R31656, R32370, H43626, H44680, R97791, R97841, H96639, N36375, AA192798, AA236435, AA262943, AA491551, AA491856, AA506260, AA533612, AA563684, AA639509, AA193170, AA453170, AA478555, AA478689, AA628811, AA971928

841146	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1411 of SEQ ID NO:652, b is an integer of 15 to 1425, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:652, and where b is greater than or equal to a + 14.	T49969, T55739, T55781, R44196, R44196, R56223, R65770, R65861, H07914, H29735, H47548, N23748, N33136, N36915, N42188, N58782, AA044179, AA044364, AA056411, AA056659, AA088892, AA129553, AA136567, AA182691, AA460927, AA461231, AA423834, AA423872, AA429008, AA284199, AA502390, AA503746, AA524414, AA573485, AA731750, AA748643, N42149, C03886, C04870, AA401440, AA443282, AA453535, AA680012, AA885303, AA773518, AA905979, AA917504, AA993697, AI014527, AI038343, AI039552, AI075983, AI040477, T15474, Z40499
841150	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 600 of SEQ ID NO:653, b is an integer of 15 to 614, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:653, and where b is greater than or equal to a + 14.	
841153	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2798 of SEQ ID NO:654, b is an integer of 15 to 2812, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:654, and where b is greater than or equal to a + 14.	
841154	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1983 of SEQ ID NO:655, b is an integer of 15 to 1997, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:655, and where b is greater than or equal to a + 14.	
841156	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1583 of SEQ ID NO:656, b is an integer of 15 to 1597, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:656, and where b is greater than or equal to a + 14.	
841157	Preferably excluded from the present invention are one or more	

	polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 358 of SEQ ID NO:657, b is an integer of 15 to 372, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:657, and where b is greater than or equal to a + 14.	
841159	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1212 of SEQ ID NO:658, b is an integer of 15 to 1226, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:658, and where b is greater than or equal to a + 14.	T68013, T68157, R10329, R21935, R22192, R22205, R22243, R22259, R22584, R36709, R37550, R37969, R56215, H12513, H16028, H42778, H42777, H43237, H49572, H54638, H62014, H62015, H87009, H96461, H99230, N20416, N21538, N26351, N26416, N31763, N32343, N57436, N68981, N76396, N94358, W47130, W47170, W47092, W47303, W56010, W56319, W57999, W58082, W72901, W80918, W80919, W96026, W96247, AA009932, AA027098, AA035781, AA055834, AA056358, AA135747, AA135791, AA243433, AA513298, AA526888, AA553702, AA564515, AA569564, AA578962, AA659038, AA664637, AA664725, AA687093, AA863102, AA865570, AA937259, AA948115, F18278, F19594, N56026, AA642679, AA205043, AA284794, AA284555, AA402214, AA402779, AA421675, AA421674, AA442253, AA477073, AA670491, F22786, AA703506, AA732970, AA854540, AA993128, AI023954, AI039979, AI041931, AI094341, T24697, R10328
841164	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 450 of SEQ ID NO:659, b is an integer of 15 to 464, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:659, and where b is greater than or equal to a + 14.	
841167	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2535 of SEQ ID NO:660, b is an integer of 15 to 2549, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:660, and where b is greater than or equal to a + 14.	
841170	Preferably excluded from the present invention are one or more	R01156, R05766, R36365, H10217, H10272, R85306, R85305,

	polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1148 of SEQ ID NO:661, b is an integer of 15 to 1162, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:661, and where b is greater than or equal to a + 14.	R92966, R94593, R94594, H87399, N30640, N62299, N67420, N75554, N95145, W69646, W69647, W87822, W87911, AA025260, AA025338, AA054320, AA054420, AA070779, AA132029, AA132151, AA147254, AA156241, AA173636, AA458647, AA458883, AA459073, AA282256, AA490721, AA491213, AA581846, AA581975, AA592924, AA617652, AA715103, AA827927, AA878469, AA922921, AA931906, AI024987, AI031704, R29605, AA641542, AA210625, AA447827, AA679290, AA845918, AA992688, AI005398, AI093117
841173	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1164 of SEQ ID NO:662, b is an integer of 15 to 1178, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:662, and where b is greater than or equal to a + 14.	T55223, T80732, R48806, R48918, H04949, H04950, H39561, AA039409, AA100837, AA128896, AA143629, AA191274, AA191696, AA223135, AA223325, AA421101, AA426158, AA910569, AA399132, AA399614, AA481845, F01004
841176	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 726 of SEQ ID NO:663, b is an integer of 15 to 740, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:663, and where b is greater than or equal to a + 14.	T57362, T57445, N98867, W04663, W58769, AA148433, AA156103, AA157650, AA157759, AA192185, AA194358, AA491525, AA492088, AA515848, AA526390, AA639064, AA575866, AA579682, AA728989, AA737291, AA740468, AA741404, AA827641, AA862841, AA932208, AA974467, AA995725, F19218, F19304, N55638, N56464, N89217, AA247353, AA401334, F20491, F20992, F21312, AA608827, F22463, F22587, AA705812, AA889507
841178	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1656 of SEQ ID NO:664, b is an integer of 15 to 1670, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:664, and where b is greater than or equal to a + 14.	
841180	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3350 of SEQ ID NO:665, b is an integer of 15 to 3364, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID	

	NO:665, and where b is greater than or equal to a + 14.	
841181	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1209 of SEQ ID NO:666, b is an integer of 15 to 1223, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:666, and where b is greater than or equal to a + 14.	
841182	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1983 of SEQ ID NO:667, b is an integer of 15 to 1997, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:667, and where b is greater than or equal to a + 14.	
841185	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 572 of SEQ ID NO:668, b is an integer of 15 to 586, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:668, and where b is greater than or equal to a + 14.	R52220, R70423, N35269, N40823, W42954, AA281810, AA524713, AA093155
841187	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1083 of SEQ ID NO:669, b is an integer of 15 to 1097, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:669, and where b is greater than or equal to a + 14.	R13459, R37369, AA814459, AA977199, AA989190, AI004908, F19612, C15655, AA203403, AA486444, AA489297, AA677279, AA775589, AA909931, AI032801, AI034230, AI040649, AI091697
841188	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2886 of SEQ ID NO:670, b is an integer of 15 to 2900, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:670, and where b is greater than or equal to a + 14.	
841189	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 973 of SEQ ID NO:671, b is an integer of 15 to 987, where both a and b	AA001736, AA132627, AA568390, F19019, W26201, W69639, W69638

	correspond to the positions of nucleotide residues shown in SEQ ID NO:671, and where b is greater than or equal to a + 14.	
841192	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2811 of SEQ ID NO:672, b is an integer of 15 to 2825, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:672, and where b is greater than or equal to a + 14.	T71550, T83900, R08468, T83730, T96865, T96866, R25503, R33010, R33895, R35402, R49701, R49701, H26757, H26856, H26871, H64273, H64272, H79029, N38824, N45452, N59621, N78174, W32994, AA022663, AA022744, AA033910, AA034030, AA210790, AA215315, AA228688, AA489044, AA552631, AA761038, AA761245, AA765845, AA805289, AA862618, AA918378, AA991204, C20951, AA476743, AA476746, AA663218, AA663792, AA706854, AI022429, AI028102, AI038738, AI051573, AI051788, AI082582, AI084275, D25731, F04009, F06746, F07761, AA701500, AA702733
841194	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1416 of SEQ ID NO:673, b is an integer of 15 to 1430, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:673, and where b is greater than or equal to a + 14.	T74233, T88950, T89868, R11972, T84649, R18375, R27737, R27738, R37065, R42578, R42578, R61382, R61424, R69423, R69553, R77025, H00275, H00276, H08524, H08525, R97851, H81046, H81141, AA429044, AA429638, AA504809, AA505159, AA552544, AA582297, AA613016, AA627349, AA639590, AA573385, AA576599, AA657983, AA804493, AA866130, AA866200, AA908911, AA908916, AA922964, AI088797, AA648981, AA649000, AA442874, AA456809, AA479714, AA479836, AA485736, AA486457, AA448038, AA431346, AA434235, AA434321, AA683236, AA779612, AA885013, AA948075, AI004354, AI039367, AI090972, AA953777, T19678, F12570, F10186
841195	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1111 of SEQ ID NO:674, b is an integer of 15 to 1125, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:674, and where b is greater than or equal to a + 14.	
841198	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1063 of SEQ ID NO:675, b is an integer of 15 to 1077, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID	

	NO:675, and where b is greater than or equal to a + 14.	
841200	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 906 of SEQ ID NO:676, b is an integer of 15 to 920, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:676, and where b is greater than or equal to a + 14.	R55754, R55738, H22912, H24090, H29740, AA232258, AA442918, Z42805, F13301
841201	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1233 of SEQ ID NO:677, b is an integer of 15 to 1247, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:677, and where b is greater than or equal to a + 14.	AA932596, D80656, D81201, D81580, C15574, AI025303, AA701535
841202	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2653 of SEQ ID NO:678, b is an integer of 15 to 2667, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:678, and where b is greater than or equal to a + 14.	
841209	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 938 of SEQ ID NO:679, b is an integer of 15 to 952, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:679, and where b is greater than or equal to a + 14.	
841210	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2295 of SEQ ID NO:680, b is an integer of 15 to 2309, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:680, and where b is greater than or equal to a + 14.	
841213	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 437 of SEQ ID NO:681, b is an integer of 15 to 451, where both a and b	AA133947

	correspond to the positions of nucleotide residues shown in SEQ ID NO:681, and where b is greater than or equal to a + 14.	
841217	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1284 of SEQ ID NO:682, b is an integer of 15 to 1298, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:682, and where b is greater than or equal to a + 14.	C17425
841219	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 845 of SEQ ID NO:683, b is an integer of 15 to 859, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:683, and where b is greater than or equal to a + 14.	
841222	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1237 of SEQ ID NO:684, b is an integer of 15 to 1251, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:684, and where b is greater than or equal to a + 14.	
841223	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2586 of SEQ ID NO:685, b is an integer of 15 to 2600, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:685, and where b is greater than or equal to a + 14.	T48001, T48881, T48882, T73986, T81100, T81151, T82458, R14770, R31779, R42540, R42540, R59226, R59286, R74588, R78473, R78539, H11611, H11700, H24632, H30034, H42336, R99669, N27968, N40733, N93719, W21125, W73346, W94235, W94237, AA026530, AA039301, AA039302, AA039611, AA234259, AA460377, AA460815, AA428913, AA429928, AA468129, AA468177, AA490801, AA602786, AA622704, AA911637, AA972558, AA973705, AA987526, AI005182, AI032242, W21787, W27428, AA654230, AA443814, AA447184, AA453411, AA453917, AA479442, AA489468, AA885138, AA904627, AA972149, AI014507, AI079892, Z39201, Z43111, D45594, D45647, F13465, F10053, AA700349
841224	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 4627 of	

	SEQ ID NO:686, b is an integer of 15 to 4641, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:686, and where b is greater than or equal to a + 14.	
841226	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 386 of SEQ ID NO:687, b is an integer of 15 to 400, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:687, and where b is greater than or equal to a + 14.	
841227	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2737 of SEQ ID NO:688, b is an integer of 15 to 2751, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:688, and where b is greater than or equal to a + 14.	
841228	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 955 of SEQ ID NO:689, b is an integer of 15 to 969, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:689, and where b is greater than or equal to a + 14.	
841231	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 965 of SEQ ID NO:690, b is an integer of 15 to 979, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:690, and where b is greater than or equal to a + 14.	
841232	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 679 of SEQ ID NO:691, b is an integer of 15 to 693, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:691, and where b is greater than or equal to a + 14.	AA187539, AA593955, AA865468, AA247589, AA292221, AA394258, AI090863, D20810
841233	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the	T86954, T87037, T91296, R11017, T78621, T79104, T84877, R00236, R00549, R06637, R27822, R27923, R35744, R45232,

	general formula of a-b, where a is any integer between 1 to 1368 of SEQ ID NO:692, b is an integer of 15 to 1382, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:692, and where b is greater than or equal to a + 14.	R45232, H21370, H21411, H51867, H60283, H60590, H67220, H99964, N28349, N30781, N41554, W47213, W47113, W67148, W67391, AA004695, AA004747, AA053562, AA053590, AA281060, AA287033, AA490978, AA586578, AA720644, AA766114, AA838572, AA907289, AA922314, AA923031, AA977015, AA975857, AI085503, AI085638, AA642438, AA399464, AA448558, AA449705, AA723708, AA781911, AA846349, AA861478, AA907377, AA907376, AA909728, AA913796, AA994740, AI017543, AI027687, AI042241, AI051442, Z41060
841234	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3084 of SEQ ID NO:693, b is an integer of 15 to 3098, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:693, and where b is greater than or equal to a + 14.	
841236	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 475 of SEQ ID NO:694, b is an integer of 15 to 489, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:694, and where b is greater than or equal to a + 14.	
841238	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1830 of SEQ ID NO:695, b is an integer of 15 to 1844, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:695, and where b is greater than or equal to a + 14.	T40324, T41188, T74964, R10059, T80454, T85689, R12791, R19812, R24766, R24982, R33136, R33288, R39060, R43570, R45243, R45498, R52595, R54047, R54048, R43570, R45243, R45498, H19030, H19321, H24420, H42322, H51876, H72225, H83771, H83913, H99717, N26245, N30134, N41682, N55555, N75922, N76940, N80564, W04682, W07687, W31765, W59945, W59946, W63652, W72530, W72085, W76498, W77868, AA081593, AA082766, AA084671, AA085794, AA088881, AA102302, AA127864, AA188946, AA188844, AA191212, AA196628, AA196960, AA631298, AA639450, AA904092, AA932353, AA961333, AA987825, AA988659, AA996270, AA205904, AA209353, AA393979, AA435659, AA453452, AA600183, AA663064, AA670333, AA774102, AA843676,

		AA854275, T03100, T03322, AI031917, AI066639, AI077924, AI078160, AI085089, T15361, T23623, T24082, Z42130, Z44535, F01670, F03604, F04096, F07839, F12754, F10361, AA700109
841239	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 591 of SEQ ID NO:696, b is an integer of 15 to 605, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:696, and where b is greater than or equal to a + 14.	R99939, H63661
841242	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 526 of SEQ ID NO:697, b is an integer of 15 to 540, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:697, and where b is greater than or equal to a + 14.	
841243	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 482 of SEQ ID NO:698, b is an integer of 15 to 496, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:698, and where b is greater than or equal to a + 14.	
841248	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 973 of SEQ ID NO:699, b is an integer of 15 to 987, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:699, and where b is greater than or equal to a + 14.	
841250	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1661 of SEQ ID NO:700, b is an integer of 15 to 1675, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:700, and where b is greater than or equal to a + 14.	
841251	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the	

	general formula of a-b, where a is any integer between 1 to 542 of SEQ ID NO:701, b is an integer of 15 to 556, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:701, and where b is greater than or equal to a + 14.	
841254	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1124 of SEQ ID NO:702, b is an integer of 15 to 1138, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:702, and where b is greater than or equal to a + 14.	AA765476, AA807570, AI056471, AI075269, T24438
841263	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1048 of SEQ ID NO:703, b is an integer of 15 to 1062, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:703, and where b is greater than or equal to a + 14.	H58432, AA996201, AA598598, AA676797
841266	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 851 of SEQ ID NO:704, b is an integer of 15 to 865, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:704, and where b is greater than or equal to a + 14.	AA194189, Z36730
841269	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1369 of SEQ ID NO:705, b is an integer of 15 to 1383, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:705, and where b is greater than or equal to a + 14.	
841272	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1141 of SEQ ID NO:706, b is an integer of 15 to 1155, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:706, and where b is greater than or equal to a + 14.	
841273	Preferably excluded from the present invention are one or more	H03779, H16233, AA026349, AA192805, AA662333, F19078,

	polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1403 of SEQ ID NO:707, b is an integer of 15 to 1417, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:707, and where b is greater than or equal to a + 14.	AA192917, AA921922, AI014904, Z30103
841276	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 934 of SEQ ID NO:708, b is an integer of 15 to 948, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:708, and where b is greater than or equal to a + 14.	
841277	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1315 of SEQ ID NO:709, b is an integer of 15 to 1329, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:709, and where b is greater than or equal to a + 14.	
841278	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 520 of SEQ ID NO:710, b is an integer of 15 to 534, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:710, and where b is greater than or equal to a + 14.	
841279	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1129 of SEQ ID NO:711, b is an integer of 15 to 1143, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:711, and where b is greater than or equal to a + 14.	R09746, R10170, R65983, R65982, AA159394
841280	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3765 of SEQ ID NO:712, b is an integer of 15 to 3779, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:712, and where b is greater than or equal to a + 14.	R09747, R10073, R33389, R33390, R53830, R53881, R62135, R62236, R68366, R68572, H00283, H00284, H02853, H03749, AA157541, AA158194, AA159297, AA548738, D82787, C02009, AA443368, AA446944, AA431753, AA770228, AA947580, AA947962, AI091589, T48513

841282	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1022 of SEQ ID NO:713, b is an integer of 15 to 1036, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:713, and where b is greater than or equal to a + 14.	T74298, R51507, R78167, H08569, N39881, N57231, AA460120, N56328, N83397, N86852, N87082, C04661, AA090325, AA095234, AA095835, AA216220, AA904685, AA905691, Z26999, F12501
841283	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 4429 of SEQ ID NO:714, b is an integer of 15 to 4443, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:714, and where b is greater than or equal to a + 14.	T58069, T58183, R14589, R23688, R24089, R27635, R30799, R31679, R31721, R41362, R44141, R41362, R44141, R72635, R72711, H02881, H17299, H17300, H44461, N33623, N49466, W15423, W39662, W52186, W58286, W58287, AA034289, AA035171, AA040731, AA041202, AA043194, AA043349, AA043596, AA047418, AA047419, AA058764, AA101975, AA112998, AA114961, AA114960, AA127933, AA126680, AA156822, AA193516, AA195626, AA256538, AA256426, AA468894, AA507356, AA507368, AA516516, AA534147, AA555266, AA594917, AA631771, AA568460, AA715240, AA838519, C04979, AA707718, AA709391, AA725438, AA928191, AI024960, AI050938, AI074716, AI078311, AI087155, AI088407, AI088592, AI089297, Z38688, Z42494, AA683480, AA693964
841286	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2085 of SEQ ID NO:715, b is an integer of 15 to 2099, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:715, and where b is greater than or equal to a + 14.	T69086, H09300, H21912, H27306, H27307, H44750, H44751, AA028928, AA031481, AA031460, AA036634, AA040943, AA043170, AA042941, AA047185, AA057349, AA128136, AA224030, AA287364, AA287502, AA493521, AA506405, AA532934, AA635612, AA635790, AA017240, AA028927, AA043023, AA084506, AA126989, AA653687, AI040204, AI095872
841287	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 560 of SEQ ID NO:716, b is an integer of 15 to 574, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:716, and where b is greater than or equal to a + 14.	
841288	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the	

	general formula of a-b, where a is any integer between 1 to 833 of SEQ ID NO:717, b is an integer of 15 to 847, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:717, and where b is greater than or equal to a + 14.	
841291	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2072 of SEQ ID NO:718, b is an integer of 15 to 2086, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:718, and where b is greater than or equal to a + 14.	
841292	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2404 of SEQ ID NO:719, b is an integer of 15 to 2418, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:719, and where b is greater than or equal to a + 14.	
841294	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2527 of SEQ ID NO:720, b is an integer of 15 to 2541, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:720, and where b is greater than or equal to a + 14.	
841296	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2157 of SEQ ID NO:721, b is an integer of 15 to 2171, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:721, and where b is greater than or equal to a + 14.	
841298	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1874 of SEQ ID NO:722, b is an integer of 15 to 1888, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:722, and where b is greater than or equal to a + 14.	
841301	Preferably excluded from the present invention are one or more	T64693, R51679, R56608, H47224, N50001, N79401, W19677,

	polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 966 of SEQ ID NO:723, b is an integer of 15 to 980, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:723, and where b is greater than or equal to a + 14.	AA143155, H59350, H69073, AA580509, AA487750, AA626464, T10911, T11398, T18502, T18605, T61708, F00905, F01050, F00254, F01055, F01138
841303	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1798 of SEQ ID NO:724, b is an integer of 15 to 1812, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:724, and where b is greater than or equal to a + 14.	T80083, R18593, R24742, R27700, R38770, R43007, R43007, H15446, H15504, H22797, H23005, H24923, N94968, W30841, W39757, W40248, W84533, AA033611, AA127942, AA127976, AA132110, AA148952, AA148953, AA513119, AA524721, AA551707, AA564773, AA662707, AA814997, AA910847, AA927433, AA886610, W05640, W19569, W22703, W39296, C04698, AA096287, C75085, AA704257, AI032787, AI075657, AI086246, F04646, F08424, F00247
841304	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 960 of SEQ ID NO:725, b is an integer of 15 to 974, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:725, and where b is greater than or equal to a + 14.	
841305	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1494 of SEQ ID NO:726, b is an integer of 15 to 1508, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:726, and where b is greater than or equal to a + 14.	
841309	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1990 of SEQ ID NO:727, b is an integer of 15 to 2004, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:727, and where b is greater than or equal to a + 14.	R62724, H42483, H71117, H71118, N92184, N94614, W39691, W45047, W49839, AA046636, AA046775, AA047446, AA047503, AA160181, AA488796, AA741383, AA746409, AA811149, AA833797, AA946892, AA999767, AA249075, AA248881, AA451825, AA454157, AA628416, AA846238, AI004357
841314	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1456 of SEQ ID NO:728, b is an integer of 15 to 1470, where both a and b	

	correspond to the positions of nucleotide residues shown in SEQ ID NO:728, and where b is greater than or equal to a + 14.	
841316	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1741 of SEQ ID NO:729, b is an integer of 15 to 1755, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:729, and where b is greater than or equal to a + 14.	
841318	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 423 of SEQ ID NO:730, b is an integer of 15 to 437, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:730, and where b is greater than or equal to a + 14.	
841321	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3649 of SEQ ID NO:731, b is an integer of 15 to 3663, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:731, and where b is greater than or equal to a + 14.	
841324	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2003 of SEQ ID NO:732, b is an integer of 15 to 2017, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:732, and where b is greater than or equal to a + 14.	T96831, AA258405, AA258750, H61868, AA828983, AA447894, T96832
841326	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1990 of SEQ ID NO:733, b is an integer of 15 to 2004, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:733, and where b is greater than or equal to a + 14.	T67169, T67170, R13400, R25161, R40914, R81373, H03937, N32627, N46428, N47847, N99904, W25263, W56840, W60329, W86618, W86691, AA062970, AA082457, AA100373, AA101448, AA126274, AA134708, AA150508, AA156712, AA157068, AA156974, AA165009, AA171491, AA171862, AA179767, AA180187, AA180497, AA179780, AA180441, AA187010, AA190353, AA195448, AA227391, AA258327, AA258536, AA262632, AA489087, AA489151, AA503664, AA523741, AA582440, AA588337, AA621830, AA621902,

		AA640554, AA568289, AA744568, AA761881, AA827997, AA847455, AA913189, AA913652, AA974509, U46229, N84275, N85488, N87880, AA641297, C21410, AA091107, AA095442, AA209417, AA219739, AA599903, AA676460, AA677610, AA678785, AA707112, AA725266, AA757097, AA779171, AA779610, AA852239, AA773175, AA993290, AI023440, AI026810, AI039755, AI082013, AI089353, AA773895
841328	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1114 of SEQ ID NO:734, b is an integer of 15 to 1128, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:734, and where b is greater than or equal to a + 14.	R93165, R93258, AA115956, AA251714, AA206198, AA676321
841329	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 758 of SEQ ID NO:735, b is an integer of 15 to 772, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:735, and where b is greater than or equal to a + 14.	
841330	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1085 of SEQ ID NO:736, b is an integer of 15 to 1099, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:736, and where b is greater than or equal to a + 14.	R22883, R66728, R78688, H95005, H95113, N27178, N39923, AA037201, AA991171, U69556, AA913589, AI085980
841333	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3205 of SEQ ID NO:737, b is an integer of 15 to 3219, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:737, and where b is greater than or equal to a + 14.	T59818, T59682, R12623, R20524, R21444, R35122, R20524, R64024, H89257, N93515, W21251, W33070, W35419, W96447, W96544, AA039907, AA043958, AA043824, AA045684, AA045685, AA088865, AA099890, AA126585, AA127996, AA128092, AA176159, AA491962, AA595337, AA610623, AA668991, AA688420, AA765329, AA768238, AA831102, AA908487, D81709, N89092, C02635, C04695, AA416971, AA469921, AA598468, AA634649, AA939133, AA995031, AI082151, AI123086, T19281
841334	Preferably excluded from the present invention are one or more	

	polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 835 of SEQ ID NO:738, b is an integer of 15 to 849, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:738, and where b is greater than or equal to a + 14.	
841335	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2055 of SEQ ID NO:739, b is an integer of 15 to 2069, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:739, and where b is greater than or equal to a + 14.	R22949, R23055, R78445, W19388, AA126774, AA133979, AA173276, AA210721, AA210826, AA287324, AA287338, AA504314, AA688155, AA829651, AA836121, AA934545, AI004681, AA205833, AA628867, AI028632, AI026835, AI075920
841336	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1553 of SEQ ID NO:740, b is an integer of 15 to 1567, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:740, and where b is greater than or equal to a + 14.	
841337	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2815 of SEQ ID NO:741, b is an integer of 15 to 2829, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:741, and where b is greater than or equal to a + 14.	
841339	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 912 of SEQ ID NO:742, b is an integer of 15 to 926, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:742, and where b is greater than or equal to a + 14.	R05977, W07729, W85962
841340	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1003 of SEQ ID NO:743, b is an integer of 15 to 1017, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:743, and where b is greater than or equal to a + 14.	T87162, T87245, R83644, H65997, W86660, W87319, AA279035, Z25793

841341	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 347 of SEQ ID NO:744, b is an integer of 15 to 361, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:744, and where b is greater than or equal to a + 14.	
841342	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1922 of SEQ ID NO:745, b is an integer of 15 to 1936, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:745, and where b is greater than or equal to a + 14.	T61211, R31792, R31806, R31842, R31858, AA463633, AA279178, AA279190, AA419400, AA482006, AA521039, AA528684, D80048, AA649649, AA651768, AA652075, AA652129, AA293205, AA293206, AA443179, AA936343
841343	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1605 of SEQ ID NO:746, b is an integer of 15 to 1619, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:746, and where b is greater than or equal to a + 14.	T72227, T92679, R30797, H88591, H97509, N22238, N28360, AA045341, AA045429, AA054480, AA058517, AA085747, AA111873, AA112181, AA128375, AA146828, AA146642, AA169595, AA194346, AA194443, AA425051, AA491535, AA491727, AA553943, AA603289, AA604115, AA618399, AA631253, AA632743, AA640345, AA565849, AA657551, AA657552, AA747335, AA888284, AA903805, AA903460, AA932251, AA932650, AI074492, W26992, W27525, AA092612, AA093936, AA095079, AA495989, AA844221, AA845438, AA897210, AA928087, AA970794, AI083509, F04554, F00612
841347	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 478 of SEQ ID NO:747, b is an integer of 15 to 492, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:747, and where b is greater than or equal to a + 14.	R14800, R25047, R59757, W23811, Z42261
841352	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 589 of SEQ ID NO:748, b is an integer of 15 to 603, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:748, and where b is greater than or equal to a + 14.	T39621, T47602, T47603, T50214, T50262, T56171, T59994, N69976, N70656, N92997, N98578, W19319, W21208, W25470, W38523, W79772, W79108, N90073, AA082281, AA083720, AA102538, AA111985, AA130519, AA130518, AA131208, AA155889, AA156193, AA157132, AA157188, AA159333, AA159346, AA159404, AA159443, AA166964, AA167042, AA425520, AA228398, AA228399, AA230245, AA420475,

		AA470507, AA470518, AA470554, AA470564, AA470784, AA480624, AA482721, AA483943, AA484448, AA492057, AA492060, AA501534, AA501688, AA501705, AA502485, AA503438, AA507807, AA522865, AA523150, AA523460, AA525078, AA531038, AA532886, AA534182, AA535479, AA541295, AA548431, AA559139, AA558899, AA559895, F16130, F17508, AA582864, AA582977, AA594817, AA600752, AA602218, AA603293, AA603440, AA614252, AA614593, AA627143, AA631240, AA639097, AA640665, AA569026, AA569795, AA573527, AA578708, AA578892, AA579475, AA580548, AA568421, AA654902, AA655027, AA657423, AA657485, AA657617, AA657745, AA657873, AA658089, AA659338, AA661580, AA662328, AA662945, AA664742, AA714342, AA721063, AA729626, AA729804, AA730697, AA737143, AA746051, AA814722, AA826140, AA838575, AA856900, AA857814, AA876960, AA879008, AA879230, AA886873, AA887104, AA888489, AA908834, AA922670, AA907193, AA931585, AA939179, AA969542, AA978087, AA988995, AI000230, AI002473, AI056486, AI066507, D45301, AI089666, AI094699, N84532, N84765, N86425, N89209, C14372, C14508, C14515, C14530, C14555, C14605, C14770, C14788, C14791, AA640945, C14863, C14868, AA090649, C14935, C15107, C15223, C15471, C15682, C15775, C15870, C15930, C15935, AA131294, AA643297, AA643298, AA643790, AA650598, AA652545, AA653802, AA653817, AA216075, AA216113, AA216340, AA249201, F20411, F20721, AA457776, AA478848, AA478850, AA479946, AA489323, AA609264, AA625634, AA669489, AA457581, F22821, AA845104, T25813, T26333, AA968927, AI080006, AI080259, D19689, T50162, T59495, F13766, AA694377
841353	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2031 of SEQ ID NO:749, b is an integer of 15 to 2045, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID	N70887, N80736, W06893, W07533, W86227, W86228, AA101268, AA877981, D79871, D81890, AA206735, AA205181, AA205255, AA205303, AA447456, AA454967, AA454966, AA778336, AA970143, T18602, D21013, Z38951, Z45683, T27468, T27472, F06030, F04572

	NO:749, and where b is greater than or equal to a + 14.	
841354	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1130 of SEQ ID NO:750, b is an integer of 15 to 1144, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:750, and where b is greater than or equal to a + 14.	H08639, W86219, AA136665, AA136781, AA256507, AA256508, AA603334, AA830237, AA978040, AA987352, AA733094, T10254, Z40940
841360	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1584 of SEQ ID NO:751, b is an integer of 15 to 1598, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:751, and where b is greater than or equal to a + 14.	
841366	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1471 of SEQ ID NO:752, b is an integer of 15 to 1485, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:752, and where b is greater than or equal to a + 14.	
841405	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1742 of SEQ ID NO:753, b is an integer of 15 to 1756, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:753, and where b is greater than or equal to a + 14.	
841526	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1781 of SEQ ID NO:754, b is an integer of 15 to 1795, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:754, and where b is greater than or equal to a + 14.	
841712	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1266 of SEQ ID NO:755, b is an integer of 15 to 1280, where both a and b	

	correspond to the positions of nucleotide residues shown in SEQ ID NO:755, and where b is greater than or equal to a + 14.	
841860	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3651 of SEQ ID NO:756, b is an integer of 15 to 3665, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:756, and where b is greater than or equal to a + 14.	
842042	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1207 of SEQ ID NO:757, b is an integer of 15 to 1221, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:757, and where b is greater than or equal to a + 14.	R27775, R80938, R81040, H25849, H30556, H39898, H43685, H84621, H85342, H85863, H97623, N20020, N24066, N27150, N34137, N74869, AA013261, AA018222, AA056554, AA075594, AA111995, AA176737, AA196064, AA514335, AA731163, AA732094, AA769189, AA877155, AA887521, AA887647, AA915962, AI017806, C03891, AA648526, AA411503, AA890618, T03509, T11362, F00065
842453	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 617 of SEQ ID NO:758, b is an integer of 15 to 631, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:758, and where b is greater than or equal to a + 14.	
842635	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2482 of SEQ ID NO:759, b is an integer of 15 to 2496, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:759, and where b is greater than or equal to a + 14.	
842927	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2034 of SEQ ID NO:760, b is an integer of 15 to 2048, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:760, and where b is greater than or equal to a + 14.	R09931, T99454, R02759, R86215, H59062, AA193428, AA193451, AA235140, Z45646
842988	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the	R18558, R33656, R33770, R41425, R41425, R62291, R62292, H00771, H03451, H03535, H11769, H12026, H16764, H16873,

	general formula of a-b, where a is any integer between 1 to 1743 of SEQ ID NO:761, b is an integer of 15 to 1757, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:761, and where b is greater than or equal to a + 14.	H25402, H25403, H25761, H25802, H26331, N27708, N33053, N35107, N36527, N48776, N62848, N77755, W48862, W48734, AA016281, AA040052, AA045034, AA151597, AA149477, AA150284, AA150386, AA421931, AA458926, AA805628, AA831459, AA862368, AA946706, AI017010, D80611, D80610, D79660, Z78342, C21502, AA428166, AA446595, AA452707, AA718983, AA722005, AA861846, AI025497, AI051843, Z24971, Z28673, Z40541, Z44707
843080	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 4434 of SEQ ID NO:762, b is an integer of 15 to 4448, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:762, and where b is greater than or equal to a + 14.	
843237	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2876 of SEQ ID NO:763, b is an integer of 15 to 2890, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:763, and where b is greater than or equal to a + 14.	
843381	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1689 of SEQ ID NO:764, b is an integer of 15 to 1703, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:764, and where b is greater than or equal to a + 14.	
843718	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 248 of SEQ ID NO:765, b is an integer of 15 to 262, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:765, and where b is greater than or equal to a + 14.	
843823	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3058 of	

	SEQ ID NO:766, b is an integer of 15 to 3072, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:766, and where b is greater than or equal to a + 14.	
844056	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1307 of SEQ ID NO:767, b is an integer of 15 to 1321, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:767, and where b is greater than or equal to a + 14.	
844325	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1518 of SEQ ID NO:768, b is an integer of 15 to 1532, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:768, and where b is greater than or equal to a + 14.	H13033, H19108, W17353
844344	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2555 of SEQ ID NO:769, b is an integer of 15 to 2569, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:769, and where b is greater than or equal to a + 14.	
844368	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1623 of SEQ ID NO:770, b is an integer of 15 to 1637, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:770, and where b is greater than or equal to a + 14.	
844408	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2471 of SEQ ID NO:771, b is an integer of 15 to 2485, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:771, and where b is greater than or equal to a + 14.	R25739, R25848, R26585, R26669, R38347, R43382, R43382, R82340, R82389, H22162, H22213, H86274, H86550, H86638, N48320, N49046, N73714, AA019818, AA122109, AA152348, AA152349, AA158712, H86273, AA595813, AA612911, AA995417, C04219, AA018291, AA442061, AA442163, AA724417, AA923788, T03807, AI038239, AI051425, Z39949, F03166, F06863, F06899, F10884
844508	Preferably excluded from the present invention are one or more	AA043997

	polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 418 of SEQ ID NO:772, b is an integer of 15 to 432, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:772, and where b is greater than or equal to a + 14.	
844867	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1034 of SEQ ID NO:773, b is an integer of 15 to 1048, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:773, and where b is greater than or equal to a + 14.	R23270, R24465, H26326, N67923, AA181941, AA187906, AA687695, AA740438, AA879229, D81116, D81140
845000	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1005 of SEQ ID NO:774, b is an integer of 15 to 1019, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:774, and where b is greater than or equal to a + 14.	R22590, H92298, W04657, W31581, W37780, W39080
845281	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2234 of SEQ ID NO:775, b is an integer of 15 to 2248, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:775, and where b is greater than or equal to a + 14.	T92139, T93566, T94885, T94933, R15017, R17377, R25556, R25791, R26489, R26511, R46713, R46790, R53266, R41457, R46790, R46713, R95961, R95995, R96764, R97692, H56545, H89870, H89871, H89871, N22103, N39443, N45521, N48555, N67524, N67561, N75299, N75567, N75882, W04741, W05590, W57992, W58076, AA001138, AA001282, AA001943, AA001919, AA027274, AA029603, AA082792, AA102442, AA101126, AA150932, AA150901, AA176661, AA176888, AA223622, AA461513, AA177059, AA229768, AA230089, AA493436, AA516126, AA528397, AA551566, AA583433, AA610274, AA613338, AA665090, AA744004, AA744054, AA770662, AA829788, AA865467, AA864190, AA878328, AA922466, AA932042, AA933800, AA935845, AA973926, AA977231, AA988822, AA992503, AA995390, AI082412, AI094769, D82171, N85713, W25970, W28703, C00856, C04813, C05281, AA648060, AA650341, AA651636, AA452618, AA453239, AA626597, AA670375, AA679935, AA722603, AA770004, AA846222, AA890020, AA927073, AA992606,

		AI034036, AI056096, T16991, T23523, T19071, F01728, F02334, F05468, F06081, F04719, F08503
845288	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1591 of SEQ ID NO:776, b is an integer of 15 to 1605, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:776, and where b is greater than or equal to a + 14.	
845750	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1794 of SEQ ID NO:777, b is an integer of 15 to 1808, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:777, and where b is greater than or equal to a + 14.	T54633, T54715, T59162, T59200, T65736, T65810, R13590, R71878, H71816, H71817, H75311, H78458, H93320, H93493, N49894, N49998, N79774, N93610, W07272, W25098, W25505, W79872, W80977, W81080, AA010657, AA010658, AA024456, AA024672, AA053380, AA053095, AA148051, AA196637, AA196919, AA223159, AA234295, AA262985, AA425287, AA425492, AA551815, AA552317, AA614604, AA617675, AA639422, AA570121, AA568154, AA847251, AA983567, AI015662, C00349, N87765, C02759, C03904, C04889, C05299, C05572, AA248273, AA290679, AA402015, AA402941, AA411366, AA411367, AA411431, AA411547, AA481876, AA482058, AI032553, AI038761, AI077405, AI088638, T16907, T16906, D31160, D31471, F02456, F02921, F02975, F06184, F06650
845809	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1470 of SEQ ID NO:778, b is an integer of 15 to 1484, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:778, and where b is greater than or equal to a + 14.	
846077	Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1329 of SEQ ID NO:779, b is an integer of 15 to 1343, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:779, and where b is greater than or equal to a + 14.	

Polynucleotide and Polypeptide Variants

[0055] The present invention is directed to variants of the polynucleotide sequence disclosed in SEQ ID NO:X or the complementary strand thereto, and/or the cDNA sequence contained in a cDNA clone contained in the deposit.

[0056] The present invention also encompasses variants of the prostate and prostate cancer polypeptide sequence disclosed in SEQ ID NO:Y, a polypeptide sequence encoded by the polynucleotide sequence in SEQ ID NO:X, and/or a polypeptide sequence encoded by the cDNA in the related cDNA clone contained in the deposit.

[0057] "Variant" refers to a polynucleotide or polypeptide differing from the polynucleotide or polypeptide of the present invention, but retaining essential properties thereof. Generally, variants are overall closely similar, and, in many regions, identical to the polynucleotide or polypeptide of the present invention.

[0058] The present invention is also directed to nucleic acid molecules which comprise, or alternatively consist of, a nucleotide sequence which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100%, identical to, for example, the nucleotide coding sequence in SEQ ID NO:X or the complementary strand thereto, the nucleotide coding sequence of the related cDNA contained in a deposited library or the complementary strand thereto, a nucleotide sequence encoding the polypeptide of SEQ ID NO:Y, a nucleotide sequence encoding a polypeptide sequence encoded by the nucleotide sequence in SEQ ID NO:X, a nucleotide sequence encoding the polypeptide encoded by the cDNA in the related cDNA contained in a deposited library, and/or polynucleotide fragments of any of these nucleic acid molecules (e.g., those fragments described herein). Polypeptides encoded by these nucleic acid molecules are also encompassed by the invention. In another embodiment, the invention encompasses nucleic acid molecules which comprise or alternatively consist of, a polynucleotide which hybridizes under stringent hybridization conditions, or alternatively, under low stringency conditions, to the nucleotide coding sequence in SEQ ID NO:X, the nucleotide coding sequence of the related cDNA clone contained in a deposited library, a nucleotide sequence encoding the polypeptide of SEQ ID NO:Y, a nucleotide sequence encoding a polypeptide sequence encoded by the nucleotide sequence in SEQ ID NO:X, a nucleotide sequence encoding the polypeptide encoded by the cDNA in the related cDNA clone contained in a deposited library, and/or polynucleotide fragments of any of these nucleic acid molecules (e.g., those

fragments described herein). Polynucleotides which hybridize to the complement of these nucleic acid molecules under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

[0059] The present invention is also directed to polypeptides which comprise, or alternatively consist of, an amino acid sequence which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to, for example, the polypeptide sequence shown in SEQ ID NO:Y, a polypeptide sequence encoded by the nucleotide sequence in SEQ ID NO:X, a polypeptide sequence encoded by the cDNA in the related cDNA clone contained in a deposited library, and/or polypeptide fragments of any of these polypeptides (e.g., those fragments described herein). Polynucleotides which hybridize to the complement of the nucleic acid molecules encoding these polypeptides under stringent hybridization conditions, or alternatively, under lower stringency conditions, are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

[0060] By a nucleic acid having a nucleotide sequence at least, for example, 95% "identical" to a reference nucleotide sequence of the present invention, it is intended that the nucleotide sequence of the nucleic acid is identical to the reference sequence except that the nucleotide sequence may include up to five point mutations per each 100 nucleotides of the reference nucleotide sequence encoding the polypeptide. In other words, to obtain a nucleic acid having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. The query sequence may be, for example, an entire sequence referred to in Table 1, an ORF (open reading frame), or any fragment specified as described herein.

[0061] As a practical matter, whether any particular nucleic acid molecule or polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a nucleotide sequence of the present invention can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. 6:237-245

(1990)). In a sequence alignment the query and subject sequences are both DNA sequences. An RNA sequence can be compared by converting U's to T's. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB alignment of DNA sequences to calculate percent identiy are: Matrix=Unitary, k-tuple=4, Mismatch Penalty=1, Joining Penalty=30, Randomization Group Length=0, Cutoff Score=1, Gap Penalty=5, Gap Size Penalty 0.05, Window Size=500 or the lenght of the subject nucleotide sequence, whichever is shorter.

[0062] If the subject sequence is shorter than the query sequence because of 5' or 3' deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for 5' and 3' truncations of the subject sequence when calculating percent identity. For subject sequences truncated at the 5' or 3' ends, relative to the query sequence, the percent identity is corrected by calculating the number of bases of the query sequence that are 5' and 3' of the subject sequence, which are not matched/aligned, as a percent of the total bases of the query sequence. Whether a nucleotide is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This corrected score is what is used for the purposes of the present invention. Only bases outside the 5' and 3' bases of the subject sequence, as displayed by the FASTDB alignment, which are not matched/aligned with the query sequence, are calculated for the purposes of manually adjusting the percent identity score.

[0063] For example, a 90 base subject sequence is aligned to a 100 base query sequence to determine percent identity. The deletions occur at the 5' end of the subject sequence and therefore, the FASTDB alignment does not show a matched/alignment of the first 10 bases at 5' end. The 10 unpaired bases represent 10% of the sequence (number of bases at the 5' and 3' ends not matched/total number of bases in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 bases were perfectly matched the final percent identity would be 90%. In another example, a 90 base subject sequence is compared with a 100 base query sequence. This time the deletions are internal deletions so that there are no bases on the 5' or 3' of the subject sequence which are not matched/aligned with the query. In this case

the percent identity calculated by FASTDB is not manually corrected. Once again, only bases 5' and 3' of the subject sequence which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to made for the purposes of the present invention.

[0064] By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a query amino acid sequence of the present invention, it is intended that the amino acid sequence of the subject polypeptide is identical to the query sequence except that the subject polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the query amino acid sequence. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a query amino acid sequence, up to 5% of the amino acid residues in the subject sequence may be inserted, deleted, (indels) or substituted with another amino acid. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

[0065] As a practical matter, whether any particular polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequence in SEQ ID NO:Y or a fragment thereof, the amino acid sequence encoded by the nucleotide sequence in SEQ ID NO:X or a fragment thereof, or the amino acid sequence encoded by the cDNA in the related cDNA clone contained in a deposited library, or a fragment thereof, can be determined conventionally using known computer programs. A preferred method for determing the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci.6:237- 245(1990)). In a sequence alignment the query and subject sequences are either both nucleotide sequences or both amino acid sequences. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter.

[0066] If the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences truncated at the N- and C-termini, relative to the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. Whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of the present invention. Only residues to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C- terminal residues of the subject sequence.

[0067] For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C- termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to made for the purposes of the present invention.

[0068] The variants may contain alterations in the coding regions, non-coding regions, or both. Especially preferred are polynucleotide variants containing alterations which produce silent substitutions, additions, or deletions, but do not alter the properties or activities of the encoded polypeptide. Nucleotide variants produced by silent substitutions due to the degeneracy of the genetic code are preferred. Moreover, variants in which less than 50, less than 40, less than 30, less than 20, less than 10, or 5-50, 5-25, 5-10, 1-5, or 1-2 amino acids are substituted, deleted, or added in any combination are also preferred. Polynucleotide variants can be produced for a variety of reasons, e.g., to optimize codon expression for a particular host (change codons in the human mRNA to those preferred by a bacterial host such as E. coli).

[0069] Naturally occurring variants are called "allelic variants," and refer to one of several alternate forms of a gene occupying a given locus on a chromosome of an organism. (Genes II, Lewin, B., ed., John Wiley & Sons, New York (1985).) These allelic variants can vary at either the polynucleotide and/or polypeptide level and are included in the present invention. Alternatively, non-naturally occurring variants may be produced by mutagenesis techniques or by direct synthesis.

[0070] Using known methods of protein engineering and recombinant DNA technology, variants may be generated to improve or alter the characteristics of the polypeptides of the present invention. For instance, as discussed herein, one or more amino acids can be deleted from the N-terminus or C-terminus of the polypeptide of the present invention without substantial loss of biological function. The authors of Ron et al., J. Biol. Chem. 268: 2984-2988 (1993), reported variant KGF proteins having heparin binding activity even after deleting 3, 8, or 27 amino-terminal amino acid residues. Similarly, Interferon gamma exhibited up to ten times higher activity after deleting 8-10 amino acid residues from the carboxy terminus of this protein. (Dobeli et al., J. Biotechnology 7:199-216 (1988).)

[0071] Moreover, ample evidence demonstrates that variants often retain a biological activity similar to that of the naturally occurring protein. For example, Gayle and coworkers (J. Biol. Chem 268:22105-22111 (1993)) conducted extensive mutational analysis of human cytokine IL-1a. They used random mutagenesis to generate over 3,500 individual IL-1a mutants that averaged 2.5 amino acid changes per variant over the entire length of the molecule. Multiple mutations were examined at every possible amino acid

position. The investigators found that "[m]ost of the molecule could be altered with little effect on either [binding or biological activity]." (See, Abstract.) In fact, only 23 unique amino acid sequences, out of more than 3,500 nucleotide sequences examined, produced a protein that significantly differed in activity from wild-type.

[0072] Furthermore, as discussed herein, even if deleting one or more amino acids from the N-terminus or C-terminus of a polypeptide results in modification or loss of one or more biological functions, other biological activities may still be retained. For example, the ability of a deletion variant to induce and/or to bind antibodies which recognize the secreted form will likely be retained when less than the majority of the residues of the secreted form are removed from the N-terminus or C-terminus. Whether a particular polypeptide lacking N- or C-terminal residues of a protein retains such immunogenic activities can readily be determined by routine methods described herein and otherwise known in the art.

[0073] Thus, the invention further includes polypeptide variants which show a functional activity (e.g., biological activity) of the polypeptide of the invention of which they are a variant. Such variants include deletions, insertions, inversions, repeats, and substitutions selected according to general rules known in the art so as have little effect on activity.

[0074] The present application is directed to nucleic acid molecules at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleic acid sequences disclosed herein or fragments thereof, (e.g., including but not limited to fragments encoding a polypeptide having the amino acid sequence of an N and/or C terminal deletion), irrespective of whether they encode a polypeptide having functional activity. This is because even where a particular nucleic acid molecule does not encode a polypeptide having functional activity, one of skill in the art would still know how to use the nucleic acid molecule, for instance, as a hybridization probe or a polymerase chain reaction (PCR) primer. Uses of the nucleic acid molecules of the present invention that do not encode a polypeptide having functional activity include, inter alia, (1) isolating a gene or allelic or splice variants thereof in a cDNA library; (2) in situ hybridization (e.g., "FISH") to metaphase chromosomal spreads to provide precise chromosomal location of the gene, as described in Verma et al., Human Chromosomes: A Manual of Basic Techniques, Pergamon Press, New York (1988); and (3) Northern Blot analysis for

detecting mRNA expression in specific tissues.

[0075] Preferred, however, are nucleic acid molecules having sequences at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleic acid sequences disclosed herein, which do, in fact, encode a polypeptide having a functional activity of a polypeptide of the invention.

[0076] Of course, due to the degeneracy of the genetic code, one of ordinary skill in the art will immediately recognize that a large number of the nucleic acid molecules having a sequence at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to, for example, the nucleic acid sequence of the cDNA in the related cDNA clone contained in a deposited library, the nucleic acid sequence referred to in Table 1 (SEQ ID NO:X), or fragments thereof, will encode polypeptides "having functional activity." In fact, since degenerate variants of any of these nucleotide sequences all encode the same polypeptide, in many instances, this will be clear to the skilled artisan even without performing the above described comparison assay. It will be further recognized in the art that, for such nucleic acid molecules that are not degenerate variants, a reasonable number will also encode a polypeptide having functional activity. This is because the skilled artisan is fully aware of amino acid substitutions that are either less likely or not likely to significantly effect protein function (e.g., replacing one aliphatic amino acid with a second aliphatic amino acid), as further described below.

[0077] For example, guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie et al., "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions," Science 247:1306-1310 (1990), wherein the authors indicate that there are two main strategies for studying the tolerance of an amino acid sequence to change.

[0078] The first strategy exploits the tolerance of amino acid substitutions by natural selection during the process of evolution. By comparing amino acid sequences in different species, conserved amino acids can be identified. These conserved amino acids are likely important for protein function. In contrast, the amino acid positions where substitutions have been tolerated by natural selection indicates that these positions are not critical for protein function. Thus, positions tolerating amino acid substitution could be modified while still maintaining biological activity of the protein.

[0079] The second strategy uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene to identify regions critical for protein function. For example, site directed mutagenesis or alanine-scanning mutagenesis (introduction of single alanine mutations at every residue in the molecule) can be used. (Cunningham and Wells, Science 244:1081-1085 (1989).) The resulting mutant molecules can then be tested for biological activity.

[0080] As the authors state, these two strategies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at certain amino acid positions in the protein. For example, most buried (within the tertiary structure of the protein) amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Moreover, tolerated conservative amino acid substitutions involve replacement of the aliphatic or hydrophobic amino acids Ala, Val, Leu and Ile; replacement of the hydroxyl residues Ser and Thr; replacement of the acidic residues Asp and Glu; replacement of the amide residues Asn and Gln, replacement of the basic residues Lys, Arg, and His; replacement of the aromatic residues Phe, Tyr, and Trp, and replacement of the small-sized amino acids Ala, Ser, Thr, Met, and Gly. Besides conservative amino acid substitution, variants of the present invention include (i) substitutions with one or more of the non-conserved amino acid residues, where the substituted amino acid residues may or may not be one encoded by the genetic code, or (ii) substitution with one or more of amino acid residues having a substituent group, or (iii) fusion of the mature polypeptide with another compound, such as a compound to increase the stability and/or solubility of the polypeptide (for example, polyethylene glycol), or (iv) fusion of the polypeptide with additional amino acids, such as, for example, an IgG Fc fusion region peptide, or leader or secretory sequence, or a sequence facilitating purification. Such variant polypeptides are deemed to be within the scope of those skilled in the art from the teachings herein.

[0081] For example, polypeptide variants containing amino acid substitutions of charged amino acids with other charged or neutral amino acids may produce proteins with improved characteristics, such as less aggregation. Aggregation of pharmaceutical formulations both reduces activity and increases clearance due to the aggregate's immunogenic activity. (Pinckard et al., Clin. Exp. Immunol. 2:331-340 (1967); Robbins

et al., Diabetes 36: 838-845 (1987); Cleland et al., Crit. Rev. Therapeutic Drug Carrier Systems 10:307-377 (1993).)

[0082] A further embodiment of the invention relates to a polypeptide which comprises the amino acid sequence of a polypeptide having an amino acid sequence which contains at least one amino acid substitution, but not more than 50 amino acid substitutions, even more preferably, not more than 40 amino acid substitutions, still more preferably, not more than 30 amino acid substitutions, and still even more preferably, not more than 20 amino acid substitutions. Of course it is highly preferable for a polypeptide to have an amino acid sequence which comprises the amino acid sequence of a polypeptide of SEQ ID NO:Y, an amino acid sequence encoded by SEQ ID NO:X, and/or the amino acid sequence encoded by the cDNA in the related cDNA clone contained in a deposited library which contains, in order of ever-increasing preference, at least one, but not more than 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acid substitutions. In specific embodiments, the number of additions, substitutions, and/or deletions in the amino acid sequence of SEQ ID NO:Y or fragments thereof (e.g., the mature form and/or other fragments described herein), an amino acid sequence encoded by SEQ ID NO:X or fragments thereof, and/or the amino acid sequence encoded by the cDNA in the related cDNA clone contained in a deposited library or fragments thereof, is 1-5, 5-10, 5-25, 5-50, 10-50 or 50-150, conservative amino acid substitutions are preferable.

Polynucleotide and Polypeptide Fragments

[0083] The present invention is also directed to polynucleotide fragments of the prostate and prostate cancer polynucleotides (nucleic acids) of the invention. In the present invention, a "polynucleotide fragment" refers, for example, to a polynucleotide having a nucleic acid sequence which: is a portion of the cDNA contained in a deposited cDNA clone; or is a portion of a polynucleotide sequence encoding the polypeptide encoded by the cDNA contained in a deposited cDNA clone; or is a portion of the polynucleotide sequence in SEQ ID NO:X or the complementary strand thereto; or is a polynucleotide sequence encoding a portion of the polypeptide of SEQ ID NO:Y; or is a polynucleotide sequence encoding a portion of a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto. The nucleotide fragments of the invention are preferably at least about 15 nt, and more preferably at least about 20 nt, still more

preferably at least about 30 nt, and even more preferably, at least about 40 nt, at least about 50 nt, at least about 75 nt, at least about 100 nt, at least about 125 nt or at least about 150 nt in length. A fragment "at least 20 nt in length," for example, is intended to include 20 or more contiguous bases from, for example, the sequence contained in the cDNA in a related cDNA clone contained in a deposited library, the nucleotide sequence shown in SEQ ID NO:X or the complementary stand thereto. In this context "about" includes the particularly recited value or a value larger or smaller by several (5, 4, 3, 2, or 1) nucleotides. These nucleotide fragments have uses that include, but are not limited to, as diagnostic probes and primers as discussed herein. Of course, larger fragments (e.g., at least 150, 175, 200, 250, 500, 600, 1000, or 2000 nucleotides in length) are also encompassed by the invention.

[0084] Moreover, representative examples of polynucleotide fragments of the invention, include, for example, fragments comprising, or alternatively consisting of, a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 651-700,701- 750, 751-800, 800-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, 2001-2050, 2051-2100, 2101-2150, 2151-2200, 2201-2250, 2251-2300, 2301-2350, 2351-2400, 2401-2450, 2451-2500, 2501-2550, 2551-2600, 2601-2650, 2651-2700, 2701-2750, 2751-2800, 2801-2850, 2851-2900, 2901-2950, 2951-3000, 3001-3050, 3051-3100, 3101-3150, 3151-3200, 3201-3250, 3251-3300, 3301-3350, 3351-3400, 3401-3450, 3451-3500, 3501-3550, and 3551 to the end of SEQ ID NO:X, or the complementary strand thereto. In this context "about" includes the particularly recited range or a range larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has a functional activity (e.g., biological activity) of the polypeptide encoded by the polynucleotide of which the sequence is a portion. More preferably, these fragments can be used as probes or primers as discussed herein. Polynucleotides which hybridize to one or more of these nucleic acid molecules under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention, as are polypeptides encoded by these polynucleotides or fragments.

[0085] Moreover, representative examples of polynucleotide fragments of the invention, include, for example, fragments comprising, or alternatively consisting of, a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 651-700,701- 750, 751-800, 800-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, 2001-2050, 2051-2100, 2101-2150, 2151-2200, 2201-2250, 2251-2300, 2301-2350, 2351-2400, 2401-2450, 2451-2500, 2501-2550, 2551-2600, 2601-2650, 2651-2700, 2701-2750, 2751-2800, 2801-2850, 2851-2900, 2901-2950, 2951-3000, 3001-3050, 3051-3100, 3101-3150, 3151-3200, 3201-3250, 3251-3300, 3301-3350, 3351-3400, 3401-3450, 3451-3500, 3501-3550, and 3551 to the end of the cDNA nucleotide sequence contained in the deposited cDNA clone, or the complementary strand thereto. In this context "about" includes the particularly recited range, or a range larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has a functional activity (e.g., biological activity) of the polypeptide encoded by the cDNA nucleotide sequence contained in the deposited cDNA clone. More preferably, these fragments can be used as probes or primers as discussed herein. Polynucleotides which hybridize to one or more of these fragments under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention, as are polypeptides encoded by these polynucleotides or fragments.

[0086] In the present invention, a "polypeptide fragment" refers to an amino acid sequence which is a portion of that contained in SEQ ID NO:Y, a portion of an amino acid sequence encoded by the polynucleotide sequence of SEQ ID NO:X, and/or encoded by the cDNA contained in the related cDNA clone contained in a deposited library. Protein (polypeptide) fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments of the invention, include, for example, fragments comprising, or alternatively consisting of, an amino acid sequence from about amino acid number 1-20, 21-40, 41-60, 61-80, 81-100, 102-120, 121-140, 141-160, 161-180, 181-200, 201-220, 221-240, 241-260, 261-280, 281-300, 301-320, 321-340,

341-360, 361-380, 381-400, 401-420, 421-440, 441-460, 461-480, 481-500, 501-520, 521-540, 541-560, 561-580, 581-600, 601-620, 621-640, 641-660, 661-680, 681-700, 701-720, 721-740, 741-760, 761-780, 781-800, 801-820, 821-840, 841-860, 861-880, 881-900, 901-920, 921-940, 941-960, 961-980, 981-1000, 1001-1020, 1021-1040, 1041-1060, 1061-1080, 1081-1100, 1101-1120, 1121-1140, 1141-1160, 1161-1180, and 1181 to the end of SEQ ID NO:Y. Moreover, polypeptide fragments of the invention may be at least about 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 100, 110, 120, 130, 140, or 150 amino acids in length. In this context "about" includes the particularly recited ranges or values, or ranges or values larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either terminus or at both termini. Polynucleotides encoding these polypeptide fragments are also encompassed by the invention.

[0087] Even if deletion of one or more amino acids from the N-terminus of a protein results in modification of loss of one or more biological functions of the protein, other functional activities (e.g., biological activities, ability to multimerize, ability to bind a ligand) may still be retained. For example, the ability of shortened muteins to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptides generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a mutein with a large number of deleted N-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

[0088] Accordingly, polypeptide fragments of the invention include the secreted protein as well as the mature form. Further preferred polypeptide fragments include the secreted protein or the mature form having a continuous series of deleted residues from the amino or the carboxy terminus, or both. For example, any number of amino acids, ranging from 1-60, can be deleted from the amino terminus of either the secreted polypeptide or the mature form. Similarly, any number of amino acids, ranging from 1-30, can be deleted from the carboxy terminus of the secreted protein or mature form. Furthermore, any

combination of the above amino and carboxy terminus deletions are preferred. Similarly, polynucleotides encoding these polypeptide fragments are also preferred.

[0089] The present invention further provides polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence of a polypeptide disclosed herein (e.g., a polypeptide of SEQ ID NO:Y, a polypeptide encoded by the polynucleotide sequence contained in SEQ ID NO:X, and/or a polypeptide encoded by the cDNA contained in the related cDNA clone contained in a deposited library). In particular, N-terminal deletions may be described by the general formula m-q, where q is a whole integer representing the total number of amino acid residues in a polypeptide of the invention (e.g., the polypeptide disclosed in SEQ ID NO:Y), and m is defined as any integer ranging from 2 to q-6. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0090] Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification of loss of one or more biological functions of the protein, other functional activities (e.g., biological activities, ability to multimerize, ability to bind a ligand) may still be retained. For example the ability of the shortened mutein to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a mutein with a large number of deleted C-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

[0091] Accordingly, the present invention further provides polypeptides having one or more residues from the carboxy terminus of the amino acid sequence of a polypeptide disclosed herein (e.g., a polypeptide of SEQ ID NO:Y, a polypeptide encoded by the polynucleotide sequence contained in SEQ ID NO:X, and/or a polypeptide encoded by the cDNA contained in deposited cDNA clone referenced in Table 1). In particular, C-terminal deletions may be described by the general formula 1-n, where n is any whole integer ranging from 6 to q-1, and where n corresponds to the position of an amino acid

residue in a polypeptide of the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0092] In addition, any of the above described N- or C-terminal deletions can be combined to produce a N- and C-terminal deleted polypeptide. The invention also provides polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues m-n of a polypeptide encoded by SEQ ID NO:X (e.g., including, but not limited to, the preferred polypeptide disclosed as SEQ ID NO:Y), and/or the cDNA in the related cDNA clone contained in a deposited library, where n and m are integers as described above. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0093] Any polypeptide sequence contained in the polypeptide of SEQ ID NO:Y, encoded by the polynucleotide sequences set forth as SEQ ID NO:X, or encoded by the cDNA in the related cDNA clone contained in a deposited library may be analyzed to determine certain preferred regions of the polypeptide. For example, the amino acid sequence of a polypeptide encoded by a polynucleotide sequence of SEQ ID NO:X, or the cDNA in a deposited cDNA clone may be analyzed using the default parameters of the DNASTAR computer algorithm (DNASTAR, Inc., 1228 S. Park St., Madison, WI 53715 USA; http://www.dnastar.com/).

[0094] Polypeptide regions that may be routinely obtained using the DNASTAR computer algorithm include, but are not limited to, Garnier-Robson alpha-regions, beta-regions, turn-regions, and coil-regions, Chou-Fasman alpha-regions, beta-regions, and turn-regions, Kyte-Doolittle hydrophilic regions and hydrophobic regions, Eisenberg alpha- and beta-amphipathic regions, Karplus-Schulz flexible regions, Emini surface-forming regions and Jameson-Wolf regions of high antigenic index. Among highly preferred polynucleotides of the invention in this regard are those that encode polypeptides comprising regions that combine several structural features, such as several (e.g., 1, 2, 3 or 4) of the features set out above.

[0095] Additionally, Kyte-Doolittle hydrophilic regions and hydrophobic regions, Emini surface-forming regions, and Jameson-Wolf regions of high antigenic index (i.e., containing four or more contiguous amino acids having an antigenic index of greater than or equal to 1.5, as identified using the default parameters of the Jameson-Wolf program) can routinely be used to determine polypeptide regions that exhibit a high degree of

potential for antigenicity. Regions of high antigenicity are determined from data by DNASTAR analysis by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an environment in which antigen recognition may occur in the process of initiation of an immune response.

[0096] Preferred polypeptide fragments of the invention are fragments comprising, or alternatively consisting of, an amino acid sequence that displays a functional activity of the polypeptide sequence of which the amino acid sequence is a fragment.

[0097] By a polypeptide demonstrating a "functional activity" is meant, a polypeptide capable of displaying one or more known functional activities associated with a full-length (complete) protein of the invention. Such functional activities include, but are not limited to, biological activity, antigenicity [ability to bind (or compete with a polypeptide for binding) to an anti-polypeptide antibody], immunogenicity (ability to generate antibody which binds to a specific polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide.

[0098] Other preferred polypeptide fragments are biologically active fragments. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

[0099] In preferred embodiments, polypeptides of the invention comprise, or alternatively consist of, one, two, three, four, five or more of the antigenic fragments of the polypeptide of SEQ ID NO:Y, or portions thereof. Polynucleotides encoding these polypeptides are also encompassed by the invention.

TABLE 4

Sequence/ Contig ID	Epitopes
574130	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 941 as residues: Ala-10 to Asp-18, Asp-20 to Cys-27, Cys-44 to Gly-52, Pro-57 to Ser-62, Pro-65 to His-72, Gln-88 to Asn-94, Pro-118 to Thr-127, Pro-129 to Thr-143, Tyr-156 to Tyr-165, Pro-167 to Leu-172, Cys-180 to Asp-185.
637706	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 942 as residues: Arg-1 to Glu-6, Lys-11 to Val-24, Pro-27 to Gln-36, Glu-49 to Gly-54, His-59 to Gly-73, Thr-86 to Ala-97, Pro-104 to Gly-113, Asp-137 to Asp-160, Arg-177 to Asn-195, Leu-203 to Asn-212, Asn-219 to Thr-231, Lys-238 to Tyr-247, Glu-249 to Asn-254, Met-269 to Asp-303, Ser-328 to Ser-336.
684310	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 944 as residues: Ala-13 to Arg-20, Glu-25 to Arg-40.
731016	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 945 as residues: Gly-13 to Leu-20, Gly-40 to Ala-45.
827771	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 946 as residues: Ala-11 to Glu-16.
828193	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 947 as residues: Gly-1 to Gly-9, Ala-15 to Ala-21.
828194	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 948 as residues: Pro-45 to Trp-53.
828199	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 949 as residues: Gly-38 to Ser-44, Leu-123 to Trp-138, His-149 to Pro-154.
828221	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 950 as residues: Lys-32 to Leu-41, Arg-119 to Tyr-124, Pro-197 to Arg-204, Asp-236 to Lys-242, Ala-290 to Tyr-296, Thr-320 to Arg-331, Asp-337 to Val-343, His-358 to Gly-368, Thr-419 to Gln-424.
828235	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 951 as residues: Pro-74 to Arg-82.
828236	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 952 as residues: Lys-10 to Gly-15, Pro-22 to Ser-27, Lys-38 to Glu-63, Lys-74 to Val-87, Met-89 to Glu-123, Lys-130 to Glu-196, Val-201 to Ala-207, Arg-251 to Lys-256, Glu-271 to Arg-279, Pro-317 to Asn-327, Lys-382 to Gln-390, Tyr-409 to Glu-415.
828237	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 953 as residues: Ala-6 to Arg-20, Glu-33 to Lys-40, Gln-45 to Leu-50, Arg-52 to Gln-72, Leu-78 to Gln-94, Gln-105 to Gln-114.
828242	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 955 as residues: Thr-1 to Trp-9, Pro-26 to Ala-32, Gly-58 to Arg-68, Gln-73 to Thr-99, Ala-191 to Asp-196, Glu-225 to Glu-234.
828248	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 957 as residues: Lys-21 to Glu-27, Thr-84 to Asp-89, His-103 to Val-109.
828250	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 958 as residues: Glu-106 to Ser-111.
828256	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 959 as residues: Gly-44 to Trp-49, Pro-90 to Ser-95, Tyr-133 to Lys-142, Trp-223 to Gly-242.
828267	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 960 as residues: Pro-1 to His-11, Arg-36 to Gly-52, Arg-62 to Gly-73, Gly-85 to Leu-96, Pro-112 to Gly-117, Ser-130 to Gly-138.
828272	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 962 as residues: Glu-1 to Gly-13, Ser-58 to Phe-65, Thr-118 to Gly-131, Gly-139 to Arg-157.
828273	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 963 as residues: Ser-1 to Pro-6, Gln-38 to Arg-43.
828290	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 964 as

	residues: Trp-61 to Cys-67.
828326	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 965 as residues: Arg-2 to Gln-11, Ala-17 to Ser-24, Arg-45 to Arg-58, Pro-60 to Gly-67, Ser-86 to Thr-92, Asn-143 to Leu-158.
828397	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 966 as residues: Arg-18 to Arg-33.
828405	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 967 as residues: Ser-50 to Leu-57, Ser-88 to Ser-99, Glu-104 to Val-112, Glu-122 to Val-127, Ile-152 to Asp-157.
828461	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 968 as residues: Ala-3 to Ala-16, Leu-25 to Pro-44, Ser-82 to Leu-88, Pro-91 to Arg-99, Pro-110 to Glu-118, Ile-120 to Lys-136, Cys-142 to Leu-149, Glu-156 to Leu-167, Arg-169 to Arg-180, Gly-197 to Pro-212, Arg-269 to Leu-283.
828482	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 969 as residues: Glu-1 to Ser-7.
828491	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 971 as residues: Arg-42 to Asn-48.
828492	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 972 as residues: Pro-28 to Lys-33, Arg-41 to Glu-47.
828494	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 973 as residues: Phe-24 to Val-32, Arg-49 to Val-55, Tyr-59 to Glu-68, Leu-72 to Asn-80.
828496	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 974 as residues: Gly-1 to Arg-8, Ser-17 to Arg-22, Arg-41 to Leu-47, Lys-49 to Lys-57, Leu-66 to Arg-73, Glu-94 to Thr-104, Arg-117 to Leu-126, Lys-184 to Asn-193, Glu-197 to Arg-216.
828498	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 975 as residues: Glu-62 to Leu-68, Ile-104 to Ser-111.
828504	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 976 as residues: Ser-14 to Pro-21.
828512	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 978 as residues: Asn-26 to Gln-36, Val-48 to Asp-62, Lys-112 to Ser-123, Val-127 to Phe-132, Phe-139 to Asp-151, Val-158 to Glu-180.
828516	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 979 as residues: Gly-14 to Gly-20, Ala-22 to Ala-33, Arg-83 to Thr-88, Arg-100 to Leu-105, Lys-130 to Lys-141.
828519	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 980 as residues: Gly-7 to Pro-13, His-20 to Ala-25.
828521	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 981 as residues: Asn-13 to His-19, Ser-37 to Arg-45.
828522	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 982 as residues: Lys-12 to Glu-19, Glu-38 to Gly-43, Pro-82 to Lys-93.
828525	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 983 as residues: Pro-23 to Pro-30, Ala-59 to Ser-64, Pro-84 to Thr-93, Pro-135 to Gly-140.
828529	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 984 as residues: Ser-15 to Gln-20, Gln-92 to Phe-113, Thr-141 to Gly-146, Val-153 to Thr-158.
828530	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 985 as residues: Pro-5 to Gln-15, Lys-23 to Leu-32.
828536	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 986 as residues: His-28 to Glu-34.
828537	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 987 as residues: Ile-28 to Leu-33, Gln-42 to Ser-52, Ser-54 to Trp-59.
828539	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 988 as residues: Ala-1 to Leu-9, Ser-19 to Thr-31.
828540	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 989 as residues: Arg-1 to Lys-12, Gly-17 to Ile-23.
828543	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 991 as residues: Ala-13 to Gln-20, Asp-33 to Asn-39.

828544	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 992 as residues: Val-15 to Asp-21.
828551	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 995 as residues: Met-12 to Pro-17.
828560	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 998 as residues: Val-8 to Arg-17.
828561	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 999 as residues: Asn-7 to Gly-20, Thr-32 to Tyr-37, Arg-57 to Gly-66.
828565	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1000 as residues: Arg-1 to Asn-18.
828566	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1001 as residues: Arg-41 to His-50, Lys-52 to Thr-60.
828567	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1002 as residues: Gln-7 to Cys-12, Pro-20 to Lys-30.
828568	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1003 as residues: Pro-10 to Glu-20, Asn-29 to Trp-37, Ala-44 to Arg-51, Gln-69 to Gly-79.
828570	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1005 as residues: Ser-16 to Leu-24.
828571	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1006 as residues: Leu-1 to Gln-17.
828574	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1007 as residues: Pro-117 to Lys-134, Gln-136 to Trp-143.
828575	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1008 as residues: Lys-6 to Ala-13.
828578	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1010 as residues: Gly-72 to Asp-81, Cys-89 to Gly-100, Lys-107 to Arg-114, Lys-119 to Gln-126, Arg-140 to Ser-160.
828580	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1011 as residues: Pro-1 to Ala-7, Lys-54 to Gln-68, Leu-81 to Gln-93.
828581	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1012 as residues: Glu-13 to Ser-21, Glu-31 to Glu-37, Lys-53 to Ala-60.
828583	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1013 as residues: Gln-1 to Gly-7, Thr-22 to Gly-31.
828585	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1014 as residues: Leu-28 to His-34.
828587	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1015 as residues: Gln-1 to Lys-8, Ser-25 to Phe-38, Thr-79 to Val-90, Arg-118 to Glu-125.
828592	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1017 as residues: Gln-12 to Gln-17, Arg-43 to Gln-49, Lys-62 to Lys-67, Glu-78 to Gly-83.
828594	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1019 as residues: Glu-9 to Gln-18.
828596	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1020 as residues: Thr-1 to His-8.
828597	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1021 as residues: Gln-12 to Trp-17, Asp-83 to Ile-97, Gln-99 to Asp-104, Thr-210 to Ser-216, Arg-279 to Thr-296.
828598	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1022 as residues: Thr-1 to Ser-7.
828601	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1023 as residues: Ile-1 to Trp-10, Thr-32 to Ser-38, Pro-49 to Gly-56, Ser-78 to Arg-83, Phe-113 to Arg-122, Leu-156 to Asp-173.
828605	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1024 as residues: Arg-6 to Pro-12.
828608	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1025 as residues: Arg-52 to Ile-59, Asp-65 to Phe-76, Lys-96 to Leu-102.
828609	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1026 as

	residues: Gly-29 to Gly-36, Lys-105 to Thr-112, Phe-134 to Asn-145, Pro-182 to Gly-190.
828610	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1027 as residues: Pro-49 to Asp-58, Lys-60 to Ile-66, Ser-68 to Glu-76, Val-95 to Asn-101, Lys-118 to Thr-124.
828617	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1028 as residues: Ser-14 to Arg-22, Leu-24 to Cys-30, Pro-35 to Gly-40.
828620	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1029 as residues: Leu-2 to Arg-10, Ala-57 to Lys-64, Lys-81 to Leu-88, Tyr-160 to Pro-169, Met-203 to Asp-216.
828623	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1032 as residues: His-38 to His-44.
828625	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1033 as residues: Ile-19 to Asn-28.
828635	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1035 as residues: Arg-3 to Arg-10.
828637	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1036 as residues: Asp-9 to Cys-15.
828639	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1037 as residues: Pro-13 to His-20.
828645	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1038 as residues: Glu-1 to Gly-10, Lys-18 to Arg-41, Ala-55 to Pro-65.
828648	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1039 as residues: Ala-12 to Asn-20, Pro-23 to Asn-28, Phe-47 to Val-52, Lys-88 to Gly-93, Tyr-113 to Asn-123.
828649	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1040 as residues: Pro-14 to Gln-29.
828651	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1041 as residues: Gly-2 to Lys-13.
828655	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1043 as residues: Val-13 to Trp-27.
828657	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1044 as residues: Glu-20 to Leu-30, Glu-79 to Gly-84, Asp-89 to Trp-96.
828660	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1045 as residues: Pro-37 to Thr-43.
828663	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1046 as residues: Ala-19 to Gly-24.
828666	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1047 as residues: His-54 to Gly-59.
828668	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1048 as residues: Pro-1 to Gly-12, Pro-30 to Leu-48.
828669	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1049 as residues: Pro-2 to Ser-7, Trp-27 to Lys-38.
828671	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1051 as residues: Asp-89 to Ile-94.
828672	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1052 as residues: Lys-16 to Ser-23.
828675	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1053 as residues: Lys-11 to His-16, Ala-26 to Ser-65.
828677	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1054 as residues: Pro-7 to Trp-13.
828678	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1055 as residues: Glu-188 to Arg-196.
828679	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1056 as residues: Asn-17 to Lys-23.
828680	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1057 as residues: Pro-7 to Glu-17, Ser-68 to Tyr-85, Ser-94 to Asn-101, Thr-122 to Arg-129, Ser-

	169 to Val-174.
828681	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1058 as residues: Asp-1 to Asp-19, Arg-27 to Leu-33.
828682	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1059 as residues: Pro-34 to Glu-39, Ala-41 to Gly-47, Glu-100 to Ser-111.
828683	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1060 as residues: Gly-7 to Val-14.
828686	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1061 as residues: Pro-15 to Glu-20, Gln-71 to Leu-84, Glu-86 to Ser-96, Glu-116 to Pro-121, Val-176 to Leu-196, Asn-216 to Ala-224.
828687	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1062 as residues: Glu-3 to Ala-13, Ile-22 to Ser-28.
828688	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1063 as residues: Asp-7 to Ala-15, Pro-34 to Ile-60, Gln-110 to Asn-117.
828689	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1064 as residues: Ser-74 to Met-96, Leu-108 to Trp-117, Gly-126 to Gly-131, Glu-161 to Asp-178, Lys-181 to Tyr-191, Arg-196 to Ser-202.
828692	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1065 as residues: Pro-73 to Thr-86, Ser-93 to Val-102, Ala-157 to Lys-162, Thr-169 to Lys-184, Asp-198 to Tyr-211.
828694	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1067 as residues: Thr-1 to Ala-10, Pro-18 to Arg-25, Ala-49 to Leu-56, Ser-104 to Arg-111.
828696	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1068 as residues: Ser-5 to Ser-10.
828699	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1070 as residues: Asp-7 to Val-17, Ala-21 to Ser-26.
828702	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1071 as residues: Val-14 to Gly-26, Ser-76 to His-87, Ile-127 to Phe-134, Pro-151 to Asn-157.
828703	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1072 as residues: Cys-58 to Ser-66.
828704	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1073 as residues: Thr-35 to Thr-42.
828706	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1074 as residues: Arg-1 to Glu-13.
828708	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1075 as residues: Asn-17 to Pro-27, Ser-46 to His-51, Leu-53 to Asp-60, Cys-62 to Ile-68.
828711	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1076 as residues: Asp-24 to Phe-31.
828712	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1077 as residues: Ser-44 to Lys-49, Glu-65 to Lys-76.
828713	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1078 as residues: Pro-1 to Asp-6, Arg-13 to Gly-26.
828714	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1079 as residues: Pro-24 to Glu-42, Gln-58 to Asp-64, Gln-80 to His-90, Pro-92 to Asp-103, Tyr-139 to Glu-153, Asp-162 to Asp-180, Glu-189 to Phe-200, Ser-203 to Gln-213, Glu-219 to Gly-224, Lys-227 to Ser-236, Pro-241 to Asn-260, Phe-275 to Ser-281, Phe-305 to Asn-314, Gln-319 to Tyr-329, Thr-341 to Ser-357, Pro-360 to Cys-365, Trp-384 to Phe-398, Gln-401 to Lys-410.
828718	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1081 as residues: Asp-70 to Leu-85, Ser-195 to Arg-205, Arg-262 to Ala-268, Asn-270 to Ala-277.
828728	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1084 as residues: Gly-12 to Val-19, Asp-38 to Gln-55, Gln-84 to Tyr-91, Gln-96 to Asp-102.
828730	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1085 as residues: Gly-142 to Arg-148, Ser-173 to Gln-178, Thr-202 to Ile-207, Leu-276 to Val-282, Pro-321 to Gly-353, Thr-355 to Glu-364, Glu-380 to Lys-385.
828732	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1086 as

	residues: Leu-8 to Lys-29, Leu-79 to Glu-86, Asn-106 to Trp-113.
828733	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1087 as residues: Lys-26 to Lys-33.
828735	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1088 as residues: Ser-10 to Pro-21, Ser-94 to Ala-111, Ala-125 to Met-142, Pro-144 to Gln-150, Asp-194 to Asn-201, Val-216 to Arg-243.
828740	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1091 as residues: Asn-12 to Leu-21, Leu-23 to Ser-28.
828742	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1092 as residues: Ser-149 to Leu-158.
828748	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1093 as residues: Pro-21 to Lys-31, Glu-46 to Thr-52, Cys-93 to Trp-100, Glu-144 to Gln-150, Gln-171 to Ser-180, Pro-205 to Trp-210, Ser-222 to Cys-228.
828752	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1095 as residues: Pro-23 to Gly-28, Ser-34 to Gly-39, Leu-44 to Arg-56, Gln-101 to Leu-112, Leu-119 to Ser-124, Lys-129 to Trp-138.
828753	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1096 as residues: Ile-1 to Gly-44.
828754	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1097 as residues: Leu-21 to Gln-27.
828757	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1098 as residues: Thr-27 to Arg-34, Tyr-40 to Trp-47, Thr-83 to Ser-90.
828761	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1099 as residues: Arg-1 to Gln-19.
828762	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1100 as residues: Phe-1 to Arg-11, Leu-48 to Lys-56.
828764	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1101 as residues: Asp-79 to Arg-84.
828765	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1102 as residues: Ala-5 to Ala-10.
828766	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1103 as residues: Gly-1 to Lys-10, Glu-21 to Leu-27, Ser-38 to Leu-43.
828768	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1105 as residues: Lys-39 to Lys-64.
828770	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1106 as residues: Ser-3 to Tyr-9.
828771	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1107 as residues: Ser-13 to Cys-21.
828772	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1108 as residues: Arg-28 to Asp-34.
828776	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1111 as residues: Pro-6 to Thr-13.
828784	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1118 as residues: Glu-6 to Leu-21, Ala-34 to Ala-40.
828785	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1119 as residues: Arg-53 to Ser-64.
828786	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1120 as residues: Thr-1 to Thr-16, Ser-32 to Lys-39.
828790	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1122 as residues: Pro-13 to Ala-21.
828791	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1123 as residues: Lys-1 to Cys-6.
828792	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1124 as residues: Arg-1 to Thr-7, Gln-12 to Gly-17.
828799	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1128 as residues: Thr-2 to Lys-8, Val-47 to Trp-52.

828802	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1130 as residues: Gly-41 to Met-47, Lys-59 to Arg-72.
828803	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1131 as residues: Arg-8 to Thr-14, Ala-51 to Ser-58, Ser-60 to Ser-79, Leu-97 to His-104.
828804	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1132 as residues: Lys-1 to Pro-12, Asn-43 to Lys-48.
828805	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1133 as residues: Glu-15 to Ser-20, Thr-28 to Arg-39.
828807	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1134 as residues: Glu-14 to Lys-19.
828821	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1142 as residues: Cys-9 to Leu-15, His-28 to Gly-36.
828825	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1145 as residues: Pro-38 to Pro-43.
828826	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1146 as residues: Ile-7 to Leu-15, Lys-18 to Ser-36, Thr-66 to Lys-72, Thr-91 to Tyr-97, Val-99 to Cys-106, Glu-154 to Lys-159, Glu-171 to Asn-176, Met-187 to Ser-192, Leu-203 to Gln-212.
828829	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1147 as residues: Ser-52 to Glu-58.
828835	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1150 as residues: Lys-89 to Ser-104.
828838	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1151 as residues: Arg-1 to Arg-11.
828840	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1152 as residues: Gly-32 to Gly-37.
828845	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1153 as residues: Asn-23 to Tyr-34.
828846	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1154 as residues: Ala-40 to Tyr-55, Glu-57 to Asn-66, Glu-74 to Asn-79.
828847	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1155 as residues: Gln-66 to Gly-77, Gly-86 to Ala-93.
828849	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1156 as residues: Arg-16 to Ser-25, Asp-97 to Pro-106, Pro-166 to Leu-176, Glu-271 to Gln-285, Thr-287 to Met-294, Ser-310 to Glu-316, Pro-330 to Gly-338, Phe-400 to Ser-415, Thr-425 to Ser-433, Lys-453 to Pro-469.
828852	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1158 as residues: Val-33 to Ser-39.
828853	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1159 as residues: Pro-25 to Ser-31, Ser-34 to Gly-41.
828857	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1160 as residues: Lys-5 to Leu-10, Ser-20 to Glu-30, Leu-32 to Thr-37.
828861	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1161 as residues: Arg-33 to Phe-38, Arg-59 to Gly-64, Pro-100 to His-121, Arg-144 to Pro-162, Gln-213 to Thr-221, Pro-262 to Trp-268, Ala-292 to Phe-302, Pro-315 to Pro-323.
828866	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1162 as residues: Cys-1 to Gln-6, Gln-79 to Ala-89, Thr-96 to Leu-102.
828872	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1163 as residues: Gly-17 to Leu-40, Ala-47 to Phe-63, Glu-66 to Val-71, Ile-75 to His-92, Glu-112 to Asn-119, Asp-122 to Arg-135, Asn-140 to Phe-152, Asn-160 to Arg-166.
828874	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1164 as residues: Arg-1 to Ala-34, Pro-41 to Pro-47, Pro-49 to Asp-57, Asn-99 to Ala-105, Met-107 to Thr-112, Lys-118 to Ser-135, Glu-145 to Ile-156, Ala-202 to Lys-209, Lys-214 to Ile-220, Ala-224 to Ala-236, Ala-239 to Pro-248, Pro-260 to Lys-270, Lys-275 to Lys-300.
828875	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1165 as residues: Pro-17 to Gly-24, His-31 to Phe-36, Glu-72 to Val-79, Val-99 to Asp-104.

828878	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1167 as residues: Ser-33 to Asp-45, Thr-48 to Glu-53, Lys-70 to Glu-75, Phe-125 to Phe-131, Asp-216 to Ile-223, Met-244 to Thr-252, Asn-272 to Leu-281, Gln-314 to Lys-320, Ala-340 to Ser-348.
828879	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1168 as residues: Ser-1 to Arg-8.
828881	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1169 as residues: Arg-1 to Lys-8, Asp-184 to Gly-190, Pro-269 to Asp-274.
828885	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1170 as residues: Glu-6 to Gly-11, Gln-34 to Ala-41, Val-62 to Gly-69, Val-79 to Glu-92, Pro-95 to Asp-100, Lys-106 to Leu-123, Asp-178 to Asn-185, His-208 to Ser-213, Glu-224 to Val-231, Gly-233 to Lys-241, Ser-254 to Ser-265, Phe-279 to Ser-285, Asn-292 to Gly-307, Lys-311 to Gly-324.
828887	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1172 as residues: Ala-1 to Lys-6, Ala-55 to Ser-60, Tyr-65 to Tyr-70, Thr-75 to Pro-84, Ser-106 to Ser-111, Asn-121 to Arg-131, Glu-145 to Pro-150, Pro-156 to His-171, Ser-188 to Leu-196, Asp-231 to His-238, Ser-276 to Arg-281, Arg-298 to Glu-307, Glu-332 to Glu-339, Tyr-355 to Thr-362, Ala-381 to Ser-392, Glu-409 to Val-422.
828891	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1174 as residues: Pro-1 to Glu-18, Gly-26 to Pro-33, Pro-66 to Gly-75, Gln-105 to Val-110, Ser-128 to Pro-134, Glu-182 to Leu-187.
828899	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1175 as residues: His-1 to Arg-11, Ser-40 to Gln-49.
828907	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1176 as residues: Ser-21 to Asp-28, Pro-30 to Cys-38, Arg-98 to His-103, Asn-118 to Ile-136, Ser-153 to Trp-161, Arg-163 to Tyr-172, Thr-174 to Ser-181.
828917	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1179 as residues: His-1 to Gln-22, Thr-27 to Phe-38.
828921	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1180 as residues: Glu-1 to Glu-6.
828922	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1181 as residues: Thr-6 to Ser-21.
828926	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1184 as residues: Gly-108 to Tyr-117.
828928	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1185 as residues: Gln-7 to Trp-13, Pro-46 to Ala-55.
828930	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1186 as residues: Glu-73 to His-79, Gly-105 to Tyr-110, Asp-161 to Asn-166, Lys-187 to Gln-196, Tyr-200 to Leu-206, Glu-222 to Met-229, Ala-252 to Ser-267, Asn-314 to Trp-323, Gly-344 to Asn-352.
828937	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1188 as residues: Met-28 to Lys-33, Asp-40 to Ala-64, Tyr-72 to Lys-85, Thr-124 to Leu-131, Ala-148 to Tyr-155.
828940	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1189 as residues: Pro-23 to Gln-29, Ile-56 to Asn-61, Lys-69 to Lys-75.
828943	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1191 as residues: Val-5 to Gly-11, Gln-26 to Asp-36, Val-93 to Lys-98, Lys-101 to Thr-124, Lys-130 to Asp-141, Thr-163 to Lys-172, Ser-195 to Ala-200, Tyr-210 to Ile-220.
828946	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1192 as residues: Arg-29 to Glu-34, Ala-74 to Leu-79, Ser-88 to Ala-96, Glu-126 to Leu-133, Glu-149 to Pro-156, Pro-177 to Asp-182.
828947	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1193 as residues: Lys-28 to Gly-40.
828956	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1194 as residues: Pro-84 to Asp-94, Ile-99 to Asn-105, Lys-131 to Lys-136, Lys-141 to Asn-146, Lys-153 to His-162, Asp-170 to Arg-179, Gln-248 to Ile-258, Thr-262 to Leu-267, Thr-270

	to Phe-279, Arg-294 to Leu-302.
828958	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1195 as residues: Cys-14 to Ser-25.
828965	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1196 as residues: Ala-29 to Leu-35, Pro-83 to Val-88.
828969	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1197 as residues: Arg-2 to Gly-8.
828971	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1198 as residues: Glu-53 to Lys-60.
828973	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1199 as residues: Ser-18 to Thr-25, His-177 to Tyr-186.
828980	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1200 as residues: Cys-4 to Glu-15.
828984	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1201 as residues: Asn-14 to Lys-19, Asp-55 to Lys-64, Thr-120 to Glu-125, Pro-149 to Gly-154, His-206 to Lys-213, Pro-242 to Arg-249, Met-269 to Glu-279, Arg-281 to Ser-287, Phe-312 to Gly-317, Arg-361 to Ser-368, Glu-374 to Gln-380, Ile-386 to Tyr-391, Glu-412 to Gln-428, Arg-435 to Val-471, Ser-483 to Lys-502, Lys-507 to Glu-517, Lys-519 to Pro-530, Ser-541 to Pro-550, Gly-567 to Lys-589, Glu-593 to Val-613, Lys-616 to Leu-636, Ser-647 to Leu-673, Pro-677 to Glu-689.
828988	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1203 as residues: Asp-60 to Lys-75.
828995	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1205 as residues: Thr-26 to Gly-33, Ser-42 to Ser-53, Pro-73 to Leu-78, Pro-101 to Gly-107, Pro-147 to Ser-157, Pro-168 to Ser-176, Ser-203 to His-208, Ser-216 to Cys-221.
829005	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1207 as residues: Pro-17 to Glu-22, Thr-129 to Lys-137, Asp-164 to Asp-170.
829009	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1208 as residues: Pro-1 to Arg-14, Pro-36 to Arg-54, Arg-61 to His-68, Arg-83 to Ile-92, Ala-95 to Arg-103, Arg-107 to Glu-114.
829012	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1210 as residues: His-6 to Ser-11, Ser-122 to Asn-128, Leu-216 to Asp-221, Ser-323 to His-328.
829013	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1211 as residues: Ile-10 to Leu-16, Pro-24 to Cys-29.
829019	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1212 as residues: Tyr-29 to Ser-42.
829020	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1213 as residues: Pro-22 to Arg-32, Leu-122 to Asp-127, Gln-134 to Tyr-140, Asp-153 to Arg-168.
829021	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1214 as residues: Ile-11 to Phe-16, Pro-38 to Ile-53.
829030	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1216 as residues: Lys-82 to Gly-87, Lys-224 to Asp-230, His-245 to Glu-253, Ser-279 to Lys-285, Val-308 to Lys-314, Arg-342 to Met-348, Lys-392 to Arg-397, His-452 to Gly-458.
829035	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1217 as residues: His-36 to Ser-43.
829051	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1221 as residues: Pro-3 to Trp-9.
829052	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1222 as residues: Ala-32 to Pro-37, Pro-57 to Trp-62, Pro-82 to Leu-93.
829057	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1223 as residues: Glu-9 to Thr-21, Leu-32 to Arg-45, Glu-49 to Ala-54, Lys-62 to Leu-68, Ala-71 to Thr-99, Leu-106 to Glu-113.
829059	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1225 as residues: Asn-2 to Ser-16.
829061	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1226 as residues: Lys-1 to Ser-7.

829062	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1227 as residues: Pro-15 to Cys-23, Pro-46 to Ala-54, Pro-71 to Gly-78, Leu-84 to Pro-92, Leu-131 to Arg-137, Ala-151 to Glu-161, Thr-215 to Leu-222, Glu-253 to Ser-261, Leu-269 to Leu-275, Asn-280 to Ser-285, Arg-292 to Glu-298, Gly-302 to Ser-309, Thr-322 to Arg-327, Lys-376 to Leu-388.
829063	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1228 as residues: Gly-12 to Ala-20, Arg-58 to Phe-68.
829064	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1229 as residues: Cys-9 to Tyr-14, Gly-35 to Thr-41, Ser-44 to Thr-49, Cys-53 to Thr-68, Leu-98 to Val-103, Ile-180 to Tyr-187, Ser-208 to Val-215.
829066	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1230 as residues: Phe-15 to Met-20.
829069	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1232 as residues: Asn-1 to Gly-12, Pro-31 to His-38, Ser-54 to Ser-59, Gly-64 to Lys-69.
829074	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1233 as residues: Leu-1 to Thr-17, Glu-38 to Gln-44, Glu-46 to Asp-55, Glu-82 to Glu-100, Lys-119 to Gly-129, Lys-147 to Ser-153, Pro-187 to Thr-210, Leu-225 to Val-233, Pro-272 to Gly-279, Arg-290 to Ser-303, Pro-311 to Lys-318, Ser-334 to Pro-356, Ser-370 to Arg-377, Gly-407 to Ser-412, Met-415 to His-423.
829077	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1234 as residues: Thr-1 to Thr-10, Asp-29 to Trp-35, His-37 to Trp-50, Lys-58 to Thr-65, Glu-77 to Glu-91, Glu-116 to Arg-128, Cys-219 to Pro-224.
829085	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1237 as residues: Arg-9 to Lys-31, Leu-66 to Lys-71, Gln-119 to Gly-131, Gln-230 to Leu-239.
829093	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1238 as residues: Gln-21 to Asp-26, Glu-178 to Asn-185, Arg-213 to Glu-218, Asp-238 to Asn-246, Val-264 to Pro-272, Val-280 to His-288.
829099	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1239 as residues: Arg-2 to Ser-8, Thr-140 to Ser-151, Val-153 to His-165, Leu-176 to Arg-182, Asp-200 to Thr-207, Asn-224 to Asp-229, Cys-239 to Ser-246.
829102	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1241 as residues: Pro-10 to Lys-19.
829103	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1242 as residues: Pro-30 to His-46, Glu-127 to Leu-133.
829104	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1243 as residues: Ser-19 to Trp-26, Lys-37 to Leu-59.
829109	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1244 as residues: Gln-22 to Ser-29.
829115	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1246 as residues: Gly-23 to Cys-29, Pro-35 to Cys-40, Gly-51 to Ser-64, Asp-108 to Arg-115, Glu-132 to Val-146, Thr-149 to Glu-155.
829120	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1249 as residues: Gly-68 to Arg-74, Pro-83 to Asn-88.
829126	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1252 as residues: Lys-18 to Lys-28.
829136	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1254 as residues: Asp-19 to His-26, Asp-127 to Gly-144, Thr-179 to Gln-194, Val-223 to Thr-229, Pro-235 to Tyr-240.
829138	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1255 as residues: Ala-23 to Glu-28, Glu-37 to Ser-46, Glu-63 to Gly-68, Gln-75 to Phe-84, Thr-91 to Ser-97, His-106 to Pro-117.
829142	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1256 as residues: Pro-21 to Thr-35.
829148	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1257 as residues: Pro-33 to Lys-40.
829149	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1258 as

	residues: His-9 to Glu-18, Arg-91 to Gly-96, Ser-124 to Asp-133, Asn-163 to Cys-172, Asn-216 to Thr-222, Thr-229 to Ile-235, Lys-238 to Glu-243.
829162	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1260 as residues: Arg-1 to Arg-6, Ala-53 to Gln-58.
829179	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1263 as residues: Gln-10 to Thr-21.
829184	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1264 as residues: Thr-76 to Val-81, Leu-88 to Pro-100, Tyr-140 to Lys-150.
829185	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1265 as residues: Pro-1 to Ser-21.
829188	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1266 as residues: Lys-11 to Trp-20, Ser-22 to Ala-27, Ile-35 to Met-51, Val-53 to Glu-69, Asn-145 to Leu-151, Asp-179 to Gln-187, Pro-280 to Ala-285, Asp-293 to Ile-300.
829190	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1267 as residues: Arg-3 to Gln-9, Pro-29 to Gln-34, Glu-98 to Asp-111.
829196	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1269 as residues: Leu-53 to Asn-62, Ala-125 to Ala-132.
829197	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1270 as residues: Leu-14 to Pro-19, Ser-25 to Ser-37.
829203	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1272 as residues: Gly-1 to Leu-9, Ser-80 to Gly-85.
829209	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1273 as residues: Ser-17 to Glu-29.
829210	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1274 as residues: Ser-13 to Tyr-18.
829214	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1275 as residues: Pro-2 to Asn-10, Lys-49 to Asn-54, Arg-91 to Asn-96, Glu-118 to Cys-125, Pro-139 to Glu-144.
829215	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1276 as residues: Asn-1 to Leu-6, Ser-27 to Pro-32.
829219	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1277 as residues: Pro-15 to Pro-25, Ala-54 to Phe-61, Ile-63 to Ser-82.
829220	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1278 as residues: Pro-1 to Ser-9, Glu-48 to Gly-54, Gly-66 to Leu-71, Pro-78 to Glu-84, Ala-108 to Gln-116, Ile-167 to Asp-172, Thr-179 to His-185.
829222	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1279 as residues: Thr-45 to Gln-51, Cys-53 to Asp-60, Gly-122 to Gly-127, Lys-136 to Gly-142, Pro-164 to Lys-172.
829223	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1280 as residues: Ile-11 to Trp-16.
829225	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1281 as residues: Lys-24 to Trp-30.
829226	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1282 as residues: Lys-48 to Lys-56, Arg-64 to Glu-79, Glu-102 to Tyr-111, Glu-159 to Cys-165, Thr-187 to Lys-193, Tyr-212 to Arg-220, Tyr-254 to Pro-262, Gly-278 to Asp-284, Pro-336 to Pro-341, Pro-441 to Gly-452, Glu-468 to Asp-480, Phe-486 to Tyr-495, Asp-498 to Asn-503.
829227	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1283 as residues: Pro-40 to Ala-46.
829231	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1284 as residues: Cys-12 to Ser-17.
829233	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1286 as residues: Pro-5 to Met-16, Ala-37 to Ala-46, Pro-70 to Leu-75.
829239	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1287 as residues: Glu-63 to Arg-70, Pro-82 to Leu-91, Arg-139 to Gln-146.
829242	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1289 as

	residues: Arg-11 to Gly-17, Lys-113 to Gly-120, Arg-163 to Ser-168, Asp-200 to His-210, Ile-217 to Ile-223, Arg-260 to Glu-266, Ser-274 to Leu-281.
829246	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1290 as residues: Arg-17 to Phe-25, Asn-27 to Asn-41, Thr-57 to Ser-69, Gln-92 to Asp-98.
829250	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1291 as residues: Ser-2 to Ile-16.
829253	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1292 as residues: Arg-10 to Arg-20, Gly-48 to Val-53, Glu-69 to Asp-76, Glu-116 to Glu-122, Glu-132 to Trp-143, Asp-166 to Asn-175, Arg-191 to Asn-197, Gln-205 to Gly-233, Lys-235 to Ala-274.
829263	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1294 as residues: Pro-1 to Arg-13, Gly-20 to Gly-27, Gly-32 to Lys-38.
829266	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1295 as residues: Lys-1 to Arg-6.
829271	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1296 as residues: Ala-7 to Thr-13, Lys-56 to Lys-66, Pro-81 to Asp-88, Glu-140 to Thr-148, Ser-158 to Gln-164, Glu-201 to Asp-207, Glu-221 to Ser-230, Pro-236 to Gly-241, Pro-243 to Arg-261, Gln-270 to Gly-286.
829273	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1297 as residues: Ser-19 to Ala-24.
829274	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1298 as residues: Pro-58 to Ser-64.
829276	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1299 as residues: Arg-5 to Glu-38.
829280	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1301 as residues: Ser-31 to Arg-36, Gln-61 to Lys-66.
829284	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1303 as residues: Arg-1 to Thr-7, Ala-9 to Arg-14, Gly-24 to Gly-29, Gly-52 to Ala-60, Arg-62 to Gly-71, Arg-84 to Asn-96, Pro-102 to Thr-107.
829287	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1305 as residues: Gln-38 to Lys-45.
829295	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1306 as residues: Pro-1 to Lys-13, Ala-32 to Gln-44.
829296	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1307 as residues: Glu-45 to Glu-59, Phe-61 to His-67, Ala-78 to Ser-85, Trp-100 to Pro-105.
829298	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1309 as residues: Phe-4 to Gln-10.
829302	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1310 as residues: Ser-17 to Trp-22, Ser-73 to Arg-80.
829320	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1312 as residues: Val-5 to Lys-18, Val-56 to Lys-64, Pro-94 to Gly-100, Phe-140 to Met-148, Glu-154 to Asp-161, Pro-182 to Cys-188, Pro-190 to Asn-197, Ala-216 to Leu-224.
829322	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1313 as residues: Pro-14 to Lys-26, Asp-31 to Lys-39, Arg-112 to Ile-120, Arg-128 to Gly-141, Lys-144 to Asp-151, Lys-159 to Gly-165, His-187 to Trp-203, Asn-246 to Ala-251, Ala-261 to Gln-266, Glu-271 to Thr-280.
829355	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1314 as residues: Ala-26 to Leu-33, Arg-120 to Phe-126, Thr-191 to Asn-203, Ser-223 to Pro-232.
829364	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1315 as residues: Arg-9 to Leu-15, Leu-67 to Ser-74, Asp-93 to Tyr-98, Leu-101 to Pro-108, Lys-117 to Thr-123, Thr-138 to Leu-143.
829946	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1319 as residues: Pro-20 to Gly-29, Gly-46 to Thr-56.
829952	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1321 as residues: Pro-11 to Glu-34, Leu-82 to Gln-88.
829954	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1322 as

	residues: Leu-32 to Val-38, Gly-75 to Ser-83, Ser-86 to Tyr-92, Lys-96 to His-104, Ser-109 to Ser-117, Gln-124 to Ser-130, Asn-132 to Asn-141, Pro-164 to Leu-178, His-187 to Gly-194, Pro-203 to Gln-217.
829955	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1323 as residues: Asp-39 to Gly-45, Asn-53 to Arg-80, Gln-85 to Gly-95, Glu-101 to Glu-111, His-132 to Gly-151, Leu-159 to Tyr-166, Ser-174 to Ser-179, His-188 to Gly-200, Gln-226 to Gly-235, Cys-255 to Gly-263.
829957	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1324 as residues: Gly-1 to Phe-12, Thr-14 to Val-22, Arg-30 to Met-37, Arg-63 to Pro-69, Arg-82 to Tyr-95, Glu-102 to Gly-109, Lys-223 to Leu-240.
829958	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1325 as residues: Arg-13 to Trp-31, Val-61 to Asn-67, Lys-87 to Arg-92, Leu-97 to Asp-109, Ser-129 to Asp-139.
829960	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1326 as residues: Ile-1 to Ser-10, Ile-26 to Pro-31, Lys-83 to Asp-89, Gly-96 to Asn-101, Pro-122 to Asn-127, Ser-224 to Ile-231, Asp-350 to Pro-356.
829966	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1327 as residues: Tyr-7 to Tyr-15, Pro-43 to Ala-52, Gln-57 to Ala-62, Asn-68 to Ala-73, Tyr-75 to Met-83.
829981	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1330 as residues: Ala-96 to Lys-111, Cys-117 to Cys-128.
829985	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1331 as residues: Arg-11 to Val-19, Ala-21 to Trp-26, Tyr-54 to Lys-76, His-107 to Gln-112.
829988	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1333 as residues: Leu-32 to Glu-43, Gly-50 to Arg-58.
829990	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1334 as residues: Ser-27 to Ser-34, Gly-41 to Val-46.
829991	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1335 as residues: Leu-15 to Gln-25.
829992	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1336 as residues: Asp-1 to Gly-8, Lys-26 to Trp-33, Pro-49 to Pro-54.
829993	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1337 as residues: Leu-3 to Ser-9.
829998	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1338 as residues: Glu-42 to Leu-47, Glu-125 to Ala-136.
830001	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1341 as residues: Gly-1 to Met-8, Ile-12 to Pro-17, Gly-77 to Ser-92.
830010	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1344 as residues: Cys-1 to Ser-6, Ala-55 to Ala-65, Pro-92 to Asn-97, Gln-100 to Pro-106, Gly-119 to Gly-125, Leu-135 to Arg-143, Ser-151 to Asp-159, Gln-164 to Ser-169, Thr-180 to Asn-186, Ser-204 to Val-216, Pro-224 to Arg-250, His-275 to Tyr-287.
830128	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1346 as residues: His-4 to Thr-10.
830129	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1347 as residues: Trp-52 to Thr-58, Arg-222 to Gly-227, Asn-255 to Asp-265, Pro-452 to Arg-458, Glu-503 to Lys-509, Gly-556 to Asn-563, Asp-628 to Glu-633, Glu-676 to Ser-697, Ala-708 to Ser-714.
830140	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1349 as residues: Gln-61 to Lys-67.
830157	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1350 as residues: Pro-1 to Arg-7, Arg-14 to Glu-24.
830195	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1351 as residues: Ser-2 to Arg-14, Ala-37 to Lys-45, Glu-60 to Leu-68, His-75 to Glu-82, Arg-92 to Ser-99, Gly-105 to Gln-110, Arg-119 to Phe-125.
830196	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1352 as residues: Lys-15 to Val-27, Glu-47 to Ile-79, Gly-83 to Phe-133, Lys-135 to Glu-142, Glu-

	174 to Ile-182, Ala-249 to Lys-257, Glu-272 to Leu-280, His-287 to Glu-294, Arg-304 to Ser-311, Gly-317 to Gln-322, Leu-372 to Lys-388, His-404 to Leu-409.
830409	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1353 as residues: Ser-4 to Ala-9.
830417	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1354 as residues: Pro-33 to Leu-39, Glu-54 to Val-59, Gly-69 to Ser-76.
830531	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1355 as residues: Lys-29 to Glu-37, Leu-126 to Gly-131, Asp-149 to Glu-159, Pro-235 to Thr-255.
830677	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1356 as residues: Leu-23 to Val-37, Glu-39 to Asp-51, Gly-66 to Arg-71, Gly-79 to Gly-85, Pro-87 to Leu-94, Gly-102 to Lys-123, Ser-135 to Asp-142, Gln-145 to Arg-158, Gln-169 to Glu-174, Ala-178 to Gln-190, Ala-196 to Glu-209, Glu-212 to Glu-220, Arg-249 to His-255, Ala-298 to Glu-309, Arg-314 to Lys-368.
831355	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1357 as residues: Lys-49 to Gln-55, Glu-83 to Lys-90, Gly-158 to Gly-164, Lys-185 to Gly-192.
831420	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1358 as residues: Ala-6 to His-19, Glu-28 to Ser-42.
831702	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1359 as residues: Gly-1 to Gly-12, Glu-23 to Gly-28, Gln-56 to Trp-62, Lys-75 to Thr-103, Arg-217 to Asp-223.
832488	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1361 as residues: Leu-52 to Thr-59, Pro-86 to Ser-92, Arg-107 to Gly-118, Lys-121 to Gly-128.
833207	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1362 as residues: Val-29 to Arg-43, Gly-66 to Arg-75, Ser-94 to Gly-99, Ser-106 to Ser-112, Asp-135 to Leu-151.
835940	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1363 as residues: Arg-9 to Gln-35, Arg-94 to Cys-104.
837105	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1365 as residues: Ser-59 to Ser-65, Gln-75 to Gln-80.
837373	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1367 as residues: Arg-48 to Tyr-58, Asp-67 to Lys-75.
837687	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1368 as residues: Gly-1 to Asp-9, Ser-40 to Lys-46, Ser-65 to Pro-72, Lys-124 to Asn-137.
837991	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1369 as residues: Lys-41 to Lys-48.
838442	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1370 as residues: Cys-7 to Glu-13, Tyr-27 to Phe-37, Phe-64 to Gly-72, Val-96 to Asp-105, Asp-111 to Ala-117, Arg-119 to Gly-125.
840541	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1371 as residues: Phe-38 to His-43, Asp-53 to Asp-61.
840543	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1372 as residues: Ala-26 to Pro-32, Ser-49 to Ala-59, Glu-106 to Arg-112, Gly-140 to Arg-149, Ala-159 to Trp-181, Glu-216 to Leu-229, Ile-243 to Ser-250, Phe-254 to Lys-259.
840563	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1374 as residues: Ala-67 to Pro-87.
840565	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1375 as residues: Gln-6 to Asn-13, Ser-29 to Lys-37, Arg-73 to Val-78.
840569	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1376 as residues: Ile-1 to Thr-6.
840570	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1377 as residues: Pro-9 to Asp-23.
840571	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1378 as residues: Gly-1 to Leu-6, Gln-13 to Ser-19.
840573	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1379 as residues: Arg-1 to Ala-7, Cys-16 to Cys-21, Arg-28 to Trp-33, Ala-36 to Gln-42, Arg-50 to Val-55, Gly-63 to Gly-74, Glu-100 to Lys-112, Lys-121 to Gln-126, Asp-132 to Leu-148,

	Ser-155 to Ser-161, Thr-167 to Ser-187, Arg-219 to Leu-228.
840574	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1380 as residues: Lys-60 to Lys-72, Asn-81 to Pro-88.
840575	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1381 as residues: Pro-1 to Arg-6, Tyr-16 to Gly-32, Ser-67 to Gly-74, Ser-95 to Gly-101, Glu-194 to Lys-218, Lys-295 to Leu-305, Met-332 to Glu-337, Leu-339 to Ala-347, Glu-353 to Leu-358, Ile-369 to Glu-375, Glu-437 to Gln-444, Glu-467 to Gly-478, Gly-481 to Gly-505.
840579	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1382 as residues: Pro-40 to Ala-50, Lys-71 to Leu-76, Glu-125 to Lys-138, Cys-153 to Ser-159, Arg-167 to Glu-173, Lys-210 to Ser-215, Asn-251 to Ser-260, Trp-289 to Ser-296, Ala-358 to Ala-363, Thr-369 to Gly-376, Asn-404 to Gly-410, Pro-425 to Glu-433, His-439 to Glu-450, Gln-470 to Ile-476, Thr-493 to Leu-499.
840580	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1383 as residues: Glu-13 to Ile-28, Pro-70 to Gly-75.
840581	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1384 as residues: Ser-1 to Gly-12, Thr-27 to Pro-36, Ser-50 to Met-56.
840605	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1385 as residues: Leu-12 to Leu-17, Glu-49 to Ser-54.
840610	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1388 as residues: Thr-19 to Lys-26, Gly-46 to Thr-52, Thr-63 to Glu-68, Gly-145 to Gly-153, Ser-236 to Thr-241, Ser-253 to Arg-263, Glu-291 to Asp-296.
840612	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1390 as residues: Arg-101 to Arg-108, Trp-119 to Ala-125, Ala-131 to Asn-138, Leu-142 to Thr-150, His-354 to Ile-370.
840622	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1392 as residues: Asp-6 to Gly-11, Ala-13 to Ser-28, His-40 to Thr-232, Arg-242 to Gly-247, Gly-268 to Gln-276.
840624	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1394 as residues: Lys-5 to Gly-12, Ala-20 to Met-26, Gly-49 to Ser-55, Pro-57 to Tyr-63.
840631	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1395 as residues: Glu-8 to Arg-24, Ser-36 to Ser-44, Phe-78 to Arg-84, Ser-116 to Trp-123, Gly-266 to Gly-274, Lys-327 to Lys-332.
840633	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1397 as residues: Ser-137 to Ala-146, Gln-165 to Gln-171.
840636	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1400 as residues: Lys-24 to Tyr-32, Tyr-42 to Lys-47, Gly-60 to Ala-66, Pro-68 to His-77.
840637	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1401 as residues: Ala-10 to Gln-16, Gly-29 to Glu-40, Arg-45 to Ser-51, Thr-62 to Pro-67.
840639	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1402 as residues: Pro-35 to Asn-48, Ser-66 to Ser-73, Asp-76 to Gly-81, Gly-115 to Glu-120, Asp-131 to Gly-147, Ser-152 to Gly-158, Pro-175 to Ser-184, Arg-206 to Asn-220.
840640	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1403 as residues: Ser-118 to Ile-123.
840650	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1404 as residues: Leu-30 to Glu-44, Gly-52 to Ala-57, Tyr-133 to Leu-140, Asp-207 to Ser-219, Gln-272 to Asn-281.
840652	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1405 as residues: Trp-33 to Gly-64.
840653	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1406 as residues: Pro-1 to Ser-6, Leu-14 to Ser-40, Leu-81 to Asp-93, Pro-125 to Phe-130, Gly-137 to Glu-148, Trp-238 to Arg-246, Gln-279 to Asp-295, Cys-305 to Pro-311.
840655	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1407 as residues: Pro-2 to His-7.
840659	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1408 as residues: Gln-1 to Val-15, Ser-21 to Gly-27, Pro-32 to Trp-42, Asn-272 to Arg-277, Pro-314 to Gln-336.

840660	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1409 as residues: Glu-1 to Asn-17.
840661	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1410 as residues: Cys-7 to Ser-20, Pro-35 to Pro-42, Pro-67 to Ile-80, Thr-94 to Met-100, Leu-122 to Cys-129.
840662	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1411 as residues: Gln-97 to Leu-102, Ala-130 to Ser-136, Ser-142 to Thr-148, Ala-180 to Ser-186, Pro-191 to Glu-198, Asn-234 to Leu-240, Ser-270 to His-280.
840663	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1412 as residues: Pro-1 to Gly-12.
840670	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1413 as residues: Gly-65 to Cys-71, Lys-81 to Gln-88, Thr-97 to Asp-106, Glu-135 to Gly-143, Pro-161 to Ala-169.
840671	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1414 as residues: Pro-4 to Thr-11, Ala-15 to Pro-20.
840672	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1415 as residues: Asp-3 to Ala-10, Val-23 to Thr-34, Gln-96 to Asp-101, Thr-118 to Gly-126, Ala-130 to Lys-140, Thr-156 to Ser-176, Pro-268 to Gln-275, Pro-296 to Gly-304, Pro-342 to Pro-348, Glu-382 to Asp-389, Met-408 to Glu-414, Pro-425 to Gln-443, Pro-457 to Tyr-478, Glu-481 to Tyr-505, Gly-514 to Arg-521, Pro-525 to Gly-547, Ala-555 to Gln-567.
840673	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1416 as residues: Ser-9 to Gly-15, Ser-57 to Arg-72, Lys-90 to Pro-111, Pro-138 to Ser-151, Asp-188 to Arg-193.
840677	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1418 as residues: Gly-17 to Asn-22, Ser-59 to Val-74, Glu-83 to Glu-89, Leu-91 to Ser-97, Glu-165 to Leu-183, Ala-197 to Ile-202, Ala-207 to Pro-212, Lys-227 to Lys-243, Pro-251 to His-258.
840678	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1419 as residues: Glu-43 to Glu-48, Gly-75 to Asp-81, Arg-92 to Ser-100, Asp-108 to Tyr-114, Ala-154 to Asn-161, Thr-266 to Gln-272.
840680	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1420 as residues: Pro-2 to Gly-8.
840691	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1421 as residues: Gln-58 to Ser-64, Asp-83 to Met-88, Ser-104 to Pro-114, Asn-137 to Ser-146, Pro-179 to Gly-185, Arg-206 to Glu-228, Gly-237 to Thr-258, Gln-269 to Asp-275.
840700	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1422 as residues: His-25 to Cys-32, Arg-46 to Glu-52.
840701	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1423 as residues: Gln-8 to Trp-13, Lys-21 to Asp-28, Ile-107 to Leu-112, Lys-125 to Trp-130, Leu-159 to Thr-164.
840702	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1424 as residues: Asp-22 to Met-37.
840705	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1425 as residues: Asp-4 to Pro-12, His-29 to Ala-39, Leu-43 to Glu-66, Asp-71 to Glu-78, Leu-84 to Asp-98, Glu-102 to Ile-121, Pro-137 to Tyr-143.
840715	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1426 as residues: Cys-1 to Gln-42.
840717	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1427 as residues: Cys-1 to Gln-6, Val-19 to Ala-24.
840718	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1428 as residues: Gln-1 to Ser-14.
840724	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1430 as residues: Cys-53 to Lys-59, Thr-61 to Cys-67, Gly-86 to Cys-93.
840725	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1431 as residues: Trp-22 to Thr-27.
840727	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1432 as

	residues: Thr-1 to Gln-8, Val-23 to Gln-28, Glu-51 to His-63, Glu-73 to Gln-91.
840731	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1433 as residues: Thr-35 to Glu-43, Leu-54 to Leu-60, Pro-89 to Gly-107, Val-109 to Gly-117, Gln-119 to Thr-125.
840733	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1434 as residues: Asp-33 to Ser-48, Pro-62 to Gly-76, Ser-80 to Gln-89, Gly-96 to Trp-109.
840734	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1435 as residues: Gln-12 to Gln-17.
840736	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1436 as residues: Arg-7 to Val-13, Leu-28 to Arg-33, Ser-69 to Gln-76.
840746	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1439 as residues: Asp-7 to Ser-13, Gln-21 to Lys-30, Gln-34 to Val-49, Glu-68 to Glu-73, Leu-79 to Leu-96, Glu-109 to Glu-115, Leu-146 to Ser-153, Leu-197 to Asn-206, Ser-218 to Glu-223, Ala-278 to Trp-283, Lys-297 to Phe-303, Ser-318 to Val-323.
840748	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1440 as residues: Lys-11 to Trp-24, Arg-30 to Ser-36, Arg-41 to Ser-55, Ser-68 to Arg-74, Leu-102 to Lys-108, Val-162 to Thr-167, Ser-188 to Lys-195, Glu-211 to His-216, Arg-253 to Arg-268, Ser-273 to Pro-279, Arg-325 to Glu-330, Lys-358 to Asp-364.
840750	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1441 as residues: Met-48 to Gln-55, Ile-64 to Arg-69.
840751	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1442 as residues: Thr-30 to Lys-37, Gln-51 to Pro-56, Thr-58 to Val-72, Lys-81 to Val-88, Glu-90 to Asp-101, Gly-107 to Pro-113, Glu-115 to Ser-120, Lys-133 to Pro-143, Gly-172 to Asn-194, Val-196 to Gly-216, Phe-221 to Gln-226, Asn-255 to Lys-260, Leu-282 to Lys-290.
840757	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1443 as residues: Arg-8 to Gln-19, Arg-25 to Lys-38, Pro-91 to Pro-97.
840760	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1445 as residues: Gly-9 to Thr-14, Tyr-23 to Asp-32, Pro-40 to Pro-46.
840781	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1447 as residues: Glu-8 to Ser-13, Ser-26 to Lys-33, Lys-45 to Ser-50, Glu-81 to Glu-92, Asn-109 to Asp-115.
840789	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1448 as residues: Val-141 to Glu-147, Met-160 to Phe-166, Ser-176 to Asn-183, Arg-203 to Arg-210.
840790	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1449 as residues: Pro-17 to Asn-25.
840791	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1450 as residues: Ser-62 to Gln-126, Ala-143 to Gly-182.
840798	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1451 as residues: Ser-87 to Gln-95.
840802	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1452 as residues: Pro-22 to Glu-30, Lys-73 to Gly-79, Met-133 to Lys-140, Arg-166 to Lys-176.
840803	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1453 as residues: Ala-3 to Pro-12, Gln-29 to Ile-39, Ser-54 to Glu-72, Glu-79 to Asp-86, Pro-140 to Asp-147, Lys-161 to Lys-184, Val-188 to Thr-195, Asp-203 to Glu-215, Gln-231 to Phe-248, Gly-271 to Thr-281, Ser-290 to Asp-302, Gly-322 to Ser-336, Pro-342 to Leu-347, Lys-370 to Arg-394, Ser-424 to Ser-431, Asp-467 to Gln-483, Lys-507 to Ser-519, Phe-522 to Ser-567, Leu-578 to Gly-583, Thr-593 to Gln-600.
840811	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1455 as residues: Ser-10 to Gln-25, Pro-108 to Lys-124.
840814	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1457 as residues: Gln-29 to Arg-36.
840825	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1459 as residues: Ala-1 to Arg-10.
840827	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1461 as residues: Gly-13 to Gly-18, Pro-34 to Thr-45, Ser-47 to Asp-56, Ser-61 to Ser-73, Gly-81 to

	Gly-89, Gly-96 to Arg-102, Asp-118 to Glu-123, Thr-126 to Ala-132, Glu-178 to Glu-184, Glu-254 to Gly-260.
840828	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1462 as residues: Trp-53 to Asn-59, Thr-106 to Thr-111.
840829	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1463 as residues: Pro-16 to Thr-23, Val-67 to Asn-73.
840831	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1464 as residues: Thr-34 to Leu-42, Pro-82 to Tyr-88.
840837	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1466 as residues: Phe-39 to Ala-44, Lys-67 to Gln-77.
840838	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1467 as residues: Arg-2 to Gly-9, Arg-38 to Lys-46, Ser-53 to Ser-73, Asp-79 to Ala-84, Leu-129 to Glu-136, Glu-202 to Arg-210, Glu-216 to Ala-231, Glu-234 to Glu-254, Lys-259 to Leu-265.
840842	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1469 as residues: Phe-20 to Gly-25, Pro-73 to His-81, Pro-84 to Gly-90, Ser-94 to Arg-100.
840843	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1470 as residues: Gln-45 to Arg-55, Glu-74 to Leu-79, Lys-97 to Lys-103, Arg-108 to Lys-114, Asp-124 to Asp-138, His-153 to Gly-174, Lys-205 to Ala-223, Glu-230 to Arg-241, Glu-249 to Arg-256.
840845	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1471 as residues: Pro-29 to Trp-37, Pro-39 to Arg-44, Thr-51 to Trp-56, Ala-63 to Pro-73.
840851	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1473 as residues: Thr-23 to Glu-30, Gly-34 to Pro-51, Ser-53 to Pro-65, Lys-68 to Asp-85, Gly-97 to Gly-105, Ser-150 to Leu-163, Gln-205 to Thr-216, Thr-221 to Ser-227, Pro-237 to Leu-242, Val-258 to Asn-269, Glu-280 to Phe-291, Gly-295 to Pro-302, Gly-324 to Pro-332, Ser-342 to Ala-353, Arg-388 to Thr-426, Ser-432 to Tyr-439, Ala-452 to Gly-510, Glu-512 to Pro-524.
840854	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1475 as residues: Met-37 to Arg-43.
840858	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1476 as residues: Glu-37 to Lys-51, Thr-85 to Gly-91, Ser-115 to Trp-121, Tyr-177 to Asn-186.
840859	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1477 as residues: Asp-1 to Gln-7, Met-27 to Val-34.
840863	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1478 as residues: Lys-41 to Ala-51.
840868	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1479 as residues: Ala-3 to Trp-16, Lys-63 to Asn-72, Gln-112 to Leu-121, Leu-153 to Asp-159, Ala-163 to Leu-168, His-180 to Asp-187, Asp-347 to Gly-352, Met-356 to Ser-364, Pro-390 to Lys-401, Ala-519 to Thr-541, Arg-549 to Lys-554.
840869	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1480 as residues: Pro-6 to Asp-12, Arg-28 to Thr-37, Ile-50 to Lys-59, Ala-63 to Gly-70, Pro-89 to Tyr-96, Ser-103 to Ile-111, Thr-114 to Phe-121, Asp-141 to Pro-147, Arg-162 to Thr-172.
840870	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1481 as residues: Pro-18 to Gly-24.
840875	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1482 as residues: Thr-29 to Asn-37, Val-58 to Thr-63, Glu-114 to Glu-120, Thr-177 to Leu-184, Leu-196 to Ser-205.
840876	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1483 as residues: Gln-2 to Thr-7, Phe-119 to Trp-125, Thr-141 to Cys-147, Asn-210 to Gly-216, Thr-248 to Val-255, Pro-291 to Arg-296, Asp-308 to Asp-316, Glu-327 to Lys-335, Ser-341 to Thr-346.
840881	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1484 as residues: Asp-1 to Pro-14, Met-24 to Val-42, Lys-44 to Ser-60, Tyr-107 to Thr-114.
840883	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1485 as residues: Pro-28 to Cys-35, Glu-37 to Gln-43, Arg-51 to Arg-58, Gly-79 to Gly-85.

840886	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1486 as residues: Arg-1 to Ser-6, Gln-45 to Gln-51.
840887	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1487 as residues: Asn-77 to Met-83.
840891	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1488 as residues: Gln-1 to His-8, Arg-16 to Gln-25, Thr-32 to Ser-42.
840892	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1489 as residues: Pro-19 to Val-29, Lys-31 to Tyr-48.
840894	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1490 as residues: Pro-48 to Leu-55, Ser-65 to Gly-70, His-93 to His-126, Ile-128 to Glu-146, Leu-151 to Trp-159, Trp-161 to Pro-170, His-177 to Ala-182.
840896	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1491 as residues: Thr-37 to Ser-51.
840897	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1492 as residues: Ser-8 to Gly-13, Cys-32 to Ser-39, Cys-59 to Gly-64, Arg-72 to Gly-78, Leu-91 to Glu-104, Gly-118 to Glu-123, Asn-140 to Gln-149, Leu-157 to Ile-173, Glu-188 to Gln-209, Asn-222 to Lys-244, Gln-294 to Ile-300, Glu-336 to Val-342, Leu-346 to Lys-355.
840898	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1493 as residues: Ala-1 to Thr-6.
840904	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1494 as residues: Arg-7 to Gly-18, Asn-33 to Trp-40, Leu-48 to Thr-54, Pro-101 to Ala-106, Lys-119 to Val-126, Lys-169 to Leu-175, Gln-205 to Asp-216, Met-232 to Val-239, Arg-241 to Glu-252, Glu-260 to Pro-276, Ser-284 to Ile-291.
840905	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1495 as residues: Pro-17 to Ala-29, Leu-57 to His-67, Tyr-131 to Gly-137, Val-148 to Ser-153, Leu-214 to Gln-225, Ser-242 to Ser-247, Gly-261 to Ser-267, Arg-281 to Pro-286, Thr-299 to Lys-304, Ile-314 to Val-320, Lys-348 to Thr-366.
840908	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1496 as residues: Phe-49 to Glu-58, Leu-71 to Pro-85, Gln-105 to Leu-110, Thr-153 to Glu-158, Glu-168 to Ser-173, Asn-192 to Lys-197, Gln-207 to Asn-264, Pro-292 to Lys-299, Gln-331 to Leu-337, Ser-355 to Gly-362, Asp-381 to Gly-387, Val-396 to Asp-403, Thr-411 to His-416, Arg-451 to Gly-457, Glu-464 to Ala-469, Asn-492 to Gly-509, Tyr-518 to Thr-526, Glu-562 to Ser-567.
840909	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1497 as residues: Pro-15 to Gly-29, Arg-34 to Ser-52.
840910	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1498 as residues: Arg-26 to Met-31.
840912	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1499 as residues: Ala-14 to His-19, Gln-31 to Thr-39, Phe-55 to Cys-60.
840916	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1500 as residues: Gly-7 to Leu-13.
840917	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1501 as residues: Ile-20 to Cys-26.
840918	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1502 as residues: Glu-59 to Thr-69, Thr-89 to Glu-96, Met-103 to Thr-110, Tyr-168 to Lys-176, Asn-196 to Ile-201, Thr-226 to Phe-235, Asp-244 to Glu-252, Lys-282 to Ser-290, Thr-325 to Thr-339, Lys-357 to Lys-362, Asn-397 to Tyr-403.
840922	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1503 as residues: Phe-1 to Lys-7.
840927	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1505 as residues: Cys-52 to Lys-57.
840928	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1506 as residues: Arg-2 to Thr-7, Gln-65 to Trp-73, Glu-103 to Glu-110, Glu-219 to Asn-227, Glu-309 to Trp-320, Asp-389 to Asp-394.
840929	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1507 as residues: Pro-1 to Arg-7, Asp-21 to Lys-43, Lys-48 to Arg-53, Gln-59 to Gln-75, Pro-81 to

	Ala-86, Asp-127 to Lys-143, Glu-191 to Arg-197.
840930	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1508 as residues: Phe-1 to Cys-8, Ala-10 to Gly-23, Gln-114 to Lys-120, Glu-129 to Phe-135, Ile-155 to Gln-160, Ser-193 to Thr-199, Asp-214 to Gly-226, Asp-236 to Gly-245, Ala-283 to Arg-288, Ala-322 to Asp-331.
840931	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1509 as residues: Leu-28 to Asp-35, Leu-59 to Ser-65, Glu-111 to Lys-117, Gln-131 to Ala-137.
840941	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1510 as residues: Pro-16 to Ser-26, Arg-41 to Gly-49, Glu-51 to Arg-64, Tyr-69 to Phe-77, Thr-82 to Asp-90, Asp-168 to Gln-173, Lys-240 to Tyr-248.
840944	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1511 as residues: Gln-1 to Asp-10, Pro-104 to Glu-113, Pro-136 to Ala-142, Asn-152 to Lys-161.
840948	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1513 as residues: Ala-21 to His-26, Pro-41 to Gln-46, Lys-56 to Glu-66.
840953	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1515 as residues: Gly-1 to Ser-8, Arg-10 to Ser-15, Leu-17 to Gly-22, Lys-115 to Ala-130, Tyr-149 to Gly-156, Asn-181 to Glu-190, Glu-252 to Glu-257, Ser-339 to Asp-347, Leu-356 to Leu-361, Ser-387 to Lys-395, Thr-470 to Ile-476.
840954	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1516 as residues: Pro-12 to Phe-17, Asn-40 to Lys-55, Ser-105 to Thr-112, Lys-154 to Trp-168, Arg-176 to Phe-184, Leu-216 to Thr-224, Leu-237 to Val-242, Ala-365 to Val-370, Pro-379 to Gly-386, Leu-424 to Gly-430, Tyr-439 to Ser-451, Lys-459 to Tyr-464, Arg-595 to Asn-606, Asp-613 to Asn-621.
840958	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1517 as residues: Ala-1 to Lys-14, Glu-18 to Lys-40, Pro-61 to Thr-68, Pro-70 to Gln-78, Tyr-82 to Gly-90.
840960	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1518 as residues: Pro-42 to Asp-47, Thr-53 to Pro-59.
840968	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1519 as residues: Gln-5 to Glu-11.
840969	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1520 as residues: Glu-40 to His-45, Tyr-59 to Gly-68, Pro-107 to Pro-112, Leu-116 to Thr-121, Asp-139 to Lys-152.
840978	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1524 as residues: Ile-14 to Asp-19.
840980	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1525 as residues: Leu-1 to Pro-9, Val-13 to Val-41, Glu-79 to Met-86, Gln-89 to Lys-97, Glu-116 to Lys-128, Ser-130 to Gln-136, Arg-152 to Gly-158, Cys-161 to Lys-171, Pro-173 to Ala-182, Cys-184 to Ala-190, Leu-200 to Ser-206, Pro-225 to Leu-252.
840982	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1526 as residues: Pro-1 to Cys-9, Lys-27 to Ser-32, Glu-58 to Val-63, Ser-78 to Val-83.
840985	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1527 as residues: Asn-6 to Leu-17, Met-23 to Asp-33, His-56 to Gln-69, Arg-82 to Asp-89, Arg-92 to Lys-97, Ala-99 to Arg-104, Glu-140 to Asp-146, Ser-173 to Tyr-178, Cys-189 to Leu-194, Val-239 to Asn-245, Glu-266 to Arg-276.
840989	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1528 as residues: Asn-72 to Ile-78, Gly-102 to Asp-109, Arg-150 to Trp-158, Phe-255 to Pro-266, Glu-272 to Lys-277.
840991	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1529 as residues: Thr-10 to Ala-17, His-24 to Leu-30, Ala-128 to Val-136.
840996	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1530 as residues: Cys-107 to Gln-112, Lys-142 to Ser-148.
840997	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1531 as residues: Ile-25 to Pro-35, Asp-37 to Thr-42, Ala-56 to Phe-71, Arg-75 to Gln-82, Thr-127 to Tyr-139.
840998	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1532 as

	residues: Lys-19 to Thr-24, Pro-35 to Gln-130.
840999	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1533 as residues: Phe-44 to Arg-53.
841000	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1534 as residues: Ala-4 to Pro-13.
841002	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1535 as residues: Pro-8 to Ser-18, His-27 to Ser-39, Pro-50 to Gly-59.
841003	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1536 as residues: Pro-24 to Glu-31.
841008	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1537 as residues: Cys-10 to Cys-16, Thr-114 to Gly-120, Asn-200 to Lys-209.
841013	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1538 as residues: Phe-58 to Asn-66, Ala-82 to Gln-88, Ser-169 to Glu-178, Pro-222 to Gly-227, Glu-283 to Glu-289, Ala-314 to Gly-321, Ile-370 to Asn-376, Lys-409 to Ala-423, Asp-444 to Arg-449, Ser-456 to Glu-463, Asn-472 to Asn-477.
841014	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1539 as residues: Asn-8 to Phe-17, Gly-58 to Asp-64, Glu-186 to Ser-191, Ala-266 to Ile-271, Thr-300 to Lys-309, Val-327 to Met-332.
841015	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1540 as residues: Tyr-17 to Thr-29, Lys-35 to Glu-40.
841019	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1542 as residues: Phe-9 to Phe-16.
841024	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1543 as residues: Ser-6 to Gly-15, Ala-90 to Gly-96, Val-119 to Trp-127, Val-147 to Lys-155, Ala-174 to Glu-181, Ala-231 to Leu-239.
841025	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1544 as residues: Leu-18 to His-27, Asp-29 to Ser-42, Glu-62 to Asn-72, Ser-76 to Glu-81.
841026	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1545 as residues: Ala-3 to Gly-10, Lys-41 to Gly-48, Pro-69 to Ser-81, Pro-92 to Thr-97, Asn-101 to Lys-110, Gly-173 to Gly-182, Arg-188 to Asn-199.
841027	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1546 as residues: Pro-1 to Arg-19, Asp-42 to Glu-48, Asp-70 to Tyr-79, Asn-81 to Gly-88, Ala-91 to Gly-98, Glu-153 to Pro-163.
841029	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1547 as residues: Arg-50 to Ser-58, Arg-66 to Asp-73, Pro-96 to Ser-102, Gln-133 to Arg-142.
841030	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1548 as residues: Ser-23 to Gln-30.
841034	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1550 as residues: Ser-56 to Lys-61.
841036	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1551 as residues: Leu-89 to Lys-102.
841039	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1552 as residues: Glu-19 to Ser-24, Ser-52 to Gly-60, Ser-67 to Gly-74, Lys-142 to Gly-148, Pro-178 to Arg-184.
841048	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1554 as residues: Met-22 to Tyr-49, Arg-60 to Thr-69, Gln-93 to Glu-111, Pro-113 to Glu-139, His-152 to Ser-162, Lys-172 to Glu-178, Ser-183 to Ile-188, Asn-191 to Arg-201, Arg-251 to Asn-259, Thr-297 to Arg-303, Val-379 to Gln-401, Ser-407 to Pro-414, Thr-428 to Lys-446.
841050	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1556 as residues: Ile-6 to Asn-15.
841052	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1557 as residues: Pro-37 to Arg-42, Asn-83 to Phe-90, Lys-187 to Cys-192, Asp-209 to Gly-215, His-236 to Lys-243, Tyr-263 to Gly-276, Thr-308 to Gly-314, Glu-346 to Asp-351.
841054	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1558 as residues: Pro-8 to Glu-18, Ala-47 to Gly-53.
841055	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1559 as

	residues: Val-13 to Leu-31.
841056	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1560 as residues: Arg-8 to Phe-13, Arg-29 to Val-36.
841060	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1561 as residues: Asp-69 to Gln-74.
841062	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1563 as residues: Gly-1 to Lys-6, Thr-10 to Lys-16, Asp-22 to Pro-35, Pro-62 to Asp-77, Ile-85 to Met-97, Leu-130 to Thr-135, Lys-206 to Gly-213, Leu-234 to Ser-242, Leu-334 to Glu-341, Ser-354 to Lys-369, Glu-398 to Lys-409, Glu-425 to Glu-477.
841063	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1564 as residues: Ala-1 to Trp-12, Glu-49 to Gly-56, Lys-99 to Thr-110, Glu-147 to Lys-154.
841067	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1565 as residues: Ser-7 to Ala-12, Gly-14 to Met-30, Lys-52 to Ala-58.
841074	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1566 as residues: Ala-1 to Gln-6, Glu-22 to Arg-30, Leu-43 to Ser-52, Glu-61 to Lys-70, Lys-75 to Glu-84, Thr-105 to Lys-110, Asp-131 to Ala-143, Ser-151 to Thr-158, Thr-200 to Asp-208.
841076	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1567 as residues: Lys-1 to Gly-6, Asp-13 to Glu-27.
841083	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1569 as residues: Leu-42 to Lys-49, Glu-63 to Ser-68, Glu-93 to Gln-98, Asn-109 to Ser-115, Met-147 to Lys-152.
841093	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1571 as residues: Pro-5 to Glu-14, Ala-84 to His-90, Thr-93 to Gly-99, Asn-124 to Val-133, Met-144 to Val-149, Thr-192 to Glu-200.
841097	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1572 as residues: Pro-46 to Glu-56, Phe-65 to Ser-73, Glu-114 to Asp-121, Thr-132 to Gln-139, Asp-171 to Pro-177, Thr-215 to Val-221.
841098	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1573 as residues: Arg-9 to Gly-14, Met-36 to Lys-57, Pro-93 to Gly-98.
841113	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1575 as residues: Gln-10 to Gly-18.
841115	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1576 as residues: Ile-1 to Lys-13, Thr-36 to Ala-42, Asn-49 to Leu-55, Phe-59 to Arg-70, Asp-80 to Arg-86, Lys-92 to Lys-98.
841117	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1578 as residues: Arg-1 to Glu-26, Thr-59 to Glu-64, Gln-69 to Met-77, Arg-79 to Ser-84, Pro-86 to Pro-97, Arg-104 to Lys-121, Ala-133 to Arg-141, Leu-162 to Ser-169.
841127	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1580 as residues: Pro-1 to Pro-12, Arg-51 to Ile-56, Lys-69 to Arg-85, Glu-115 to Arg-122, Gly-129 to Gln-134, Lys-138 to Lys-156, Gly-163 to Pro-170.
841128	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1581 as residues: Pro-75 to Glu-91, Glu-121 to Gly-126, Ile-149 to Lys-155, Ala-185 to Asp-201, Glu-237 to Gly-252, Leu-256 to Ser-276.
841134	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1584 as residues: Lys-43 to Leu-48, Lys-54 to Ala-62, Asn-75 to Ala-82, Glu-135 to Asp-140, Glu-173 to Leu-178, Lys-213 to Tyr-222.
841138	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1587 as residues: Arg-68 to Gln-74, Ser-85 to Asp-115, Arg-133 to Lys-144, Arg-152 to Ile-165, Pro-184 to Lys-191, Leu-198 to Lys-215, Val-235 to Glu-240, Asp-246 to Asn-266, Glu-284 to Pro-292.
841141	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1589 as residues: Pro-16 to Glu-27, Pro-36 to Phe-43, Asn-71 to Ser-84, Thr-107 to Ser-115, Glu-147 to Lys-161, Pro-167 to Ser-185, Ser-187 to Ser-206.
841145	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1591 as residues: Glu-33 to Pro-40, Arg-48 to Pro-56, Met-71 to Gly-76, Ser-103 to Arg-115.
841146	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1592 as

	residues: Lys-21 to Thr-26, Thr-37 to Pro-42.
841150	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1593 as residues: Ser-56 to Thr-62.
841153	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1594 as residues: Glu-4 to Trp-9.
841154	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1595 as residues: Asp-24 to Tyr-29, Ser-34 to Asn-42, Leu-45 to Lys-61, Thr-117 to Ser-124, Lys-153 to Asp-158, Glu-174 to Lys-180, Leu-188 to Gly-204, Ala-220 to Leu-227, Gly-262 to His-268, Lys-276 to Thr-287, Phe-307 to Pro-319, Thr-345 to Met-351, Gln-427 to Ala-432, Asp-438 to Gln-443.
841156	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1596 as residues: Glu-4 to Gly-12, Thr-21 to Gln-27, Pro-40 to Ser-47, Pro-50 to Ser-61, Val-101 to Cys-107, Lys-138 to Gly-147, Gln-150 to Tyr-156, Lys-169 to Thr-174.
841157	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1597 as residues: Val-35 to Ala-41, Gln-56 to Trp-70.
841159	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1598 as residues: Gln-1 to Arg-7, Arg-14 to Glu-22, Ala-43 to Asp-55, Thr-65 to Arg-71.
841164	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1599 as residues: Arg-1 to Cys-11, Arg-18 to Arg-25, Glu-83 to Glu-88, Gly-108 to Lys-113.
841167	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1600 as residues: Arg-16 to Asp-22.
841170	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1601 as residues: Ala-1 to Ala-14, Ala-37 to Asp-45, Thr-55 to Leu-62, Glu-76 to Gly-82, Ile-101 to Gly-110, Pro-119 to Gly-127, Pro-129 to Asp-142, Lys-196 to Ser-210, Pro-216 to Tyr-246.
841173	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1602 as residues: Arg-52 to Gln-57, Asp-181 to Gly-187, Ser-260 to Val-271, Lys-285 to Asp-290.
841178	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1604 as residues: Ser-1 to Ala-9, Ala-14 to Ile-30, Pro-41 to Ser-50, Asn-56 to Arg-63, Asp-95 to Lys-102, Pro-126 to Ser-132.
841181	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1606 as residues: Thr-3 to Arg-12.
841182	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1607 as residues: Gly-12 to Gln-26, Cys-34 to Gly-49, Glu-86 to Tyr-93, Phe-103 to Thr-139, Asp-145 to Gln-153, Tyr-167 to Arg-176, Ser-192 to Gly-200, Ala-219 to Gly-226, Glu-234 to Trp-242.
841187	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1609 as residues: Glu-1 to Gly-15, Pro-23 to Val-48, Pro-58 to Glu-63, Thr-79 to Trp-91, Asn-203 to Lys-213.
841188	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1610 as residues: Arg-1 to Gly-7, Ile-92 to Tyr-98, Arg-153 to Gly-159, Ala-319 to Ser-324, Lys-350 to Glu-359.
841189	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1611 as residues: Arg-13 to Ala-21, Thr-29 to Arg-34, Glu-41 to Ala-50, Ser-65 to Glu-71, Glu-108 to Glu-117, Ile-144 to Arg-154, Gly-159 to His-186, Lys-189 to Tyr-197.
841192	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1612 as residues: Gln-56 to Leu-63, Gln-188 to Lys-193, His-200 to Gly-205, Leu-208 to Asn-215, Thr-358 to Lys-367, Lys-369 to Gln-377, His-426 to Arg-431, Tyr-437 to Glu-446, Glu-459 to Pro-476.
841194	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1613 as residues: Phe-54 to Ser-59, Thr-63 to Asp-69.
841195	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1614 as residues: His-1 to Gln-6, Ala-66 to Gly-79, Leu-88 to Asp-95, Glu-121 to Ile-126, Pro-140 to Pro-147, Ile-173 to Trp-180, Asn-195 to Tyr-206.
841198	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1615 as residues: Gln-29 to Arg-34, Thr-65 to Thr-76, Arg-100 to Arg-108, Leu-163 to Ala-173.
841201	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1617 as

	residues: Gln-3 to Lys-10, Pro-42 to Pro-50, Ser-66 to Ser-80, Glu-107 to Ala-121.
841202	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1618 as residues: Ser-11 to Trp-23, Glu-25 to Gly-32, Ala-56 to Gly-67, Glu-80 to Pro-96, Ala-166 to Leu-177, Asn-222 to His-231, Met-239 to Gly-249, Gly-318 to Pro-338.
841209	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1619 as residues: Arg-4 to Leu-27, Gln-63 to Leu-82, Pro-168 to Ser-175.
841213	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1621 as residues: Val-17 to Tyr-22, Cys-32 to Asp-49, Ser-104 to Pro-114.
841219	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1623 as residues: Leu-10 to Glu-28, Lys-54 to Gln-60.
841222	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1624 as residues: Ile-9 to Ser-14, Pro-68 to Cys-80, Ser-82 to Thr-87, Ile-136 to His-155, Lys-214 to Asn-224.
841223	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1625 as residues: Pro-12 to Glu-17.
841226	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1627 as residues: Ala-40 to Thr-52.
841227	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1628 as residues: Val-54 to Asn-60, Glu-81 to Thr-87, Asn-103 to Glu-108, Asn-163 to His-168, Ile-170 to Tyr-175.
841233	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1632 as residues: Gly-8 to Gly-20, Ser-81 to Phe-89, Leu-135 to Gln-140, Glu-156 to Tyr-168.
841234	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1633 as residues: Lys-65 to Phe-70, Asp-99 to Ile-104, Arg-122 to Asp-128, Leu-244 to Ile-250, Leu-258 to Leu-268, Ala-270 to Lys-286, Lys-310 to Asp-318, Asn-338 to Gln-344, Asp-360 to Leu-369, Lys-414 to Gln-422, Glu-435 to Arg-449, Lys-471 to Phe-476, Arg-498 to Leu-505, Ala-526 to Gly-534, Ala-536 to Pro-559, Pro-586 to Tyr-612, Tyr-624 to Tyr-629, Gln-639 to Gln-668.
841236	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1634 as residues: Lys-5 to Pro-18, Glu-24 to Ser-36, Pro-57 to Gly-63.
841239	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1636 as residues: Arg-1 to Ser-6.
841243	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1638 as residues: Gln-1 to Asp-7, Pro-26 to Ser-31, Leu-41 to Arg-46, Gly-57 to Thr-65, Lys-71 to Lys-76.
841248	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1639 as residues: Ala-8 to Thr-23, Pro-35 to Met-41, Asn-60 to Thr-65, Asn-89 to Glu-94, Pro-161 to Leu-167, Asp-184 to Trp-189, Phe-192 to Leu-206, Arg-215 to Leu-221.
841250	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1640 as residues: Asn-13 to Gly-22, Gln-24 to Lys-29, Ser-44 to Gly-51, Thr-128 to Asp-138, Glu-166 to Leu-175, Arg-187 to Ala-192, Pro-240 to Ala-256, Ser-259 to Trp-265, Met-281 to Lys-288, Leu-318 to Trp-356, Ser-379 to Thr-385, Phe-409 to Tyr-419.
841251	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1641 as residues: Arg-13 to Phe-20, His-22 to Ser-27, Gln-70 to Phe-76.
841254	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1642 as residues: Thr-1 to Lys-15, Gln-41 to Glu-46.
841263	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1643 as residues: Ser-27 to Arg-35, Leu-76 to Trp-85, Arg-112 to Thr-118.
841269	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1645 as residues: Lys-12 to Lys-19.
841273	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1647 as residues: Tyr-3 to Asn-9.
841277	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1649 as residues: Pro-55 to Ser-62, Arg-124 to Ile-129, Arg-145 to Asn-151, Asn-186 to Asn-196, Lys-267 to Lys-274, Arg-368 to Arg-373.
841278	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1650 as

	residues: Ala-6 to Pro-13, Asn-19 to Phe-24.
841279	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1651 as residues: Thr-3 to Gly-12, Arg-19 to Ala-24, Arg-30 to Gly-43, Pro-46 to Trp-51, Gly-77 to Arg-85.
841280	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1652 as residues: Ser-14 to Thr-20, Glu-44 to Gly-50, Lys-68 to Pro-76, Glu-91 to Glu-96, Ala-110 to Lys-116, Lys-124 to His-131, Gly-164 to Gln-173, Leu-191 to Asn-200, Met-215 to Ser-221, Gln-236 to Lys-258, Pro-266 to Asn-271, Pro-279 to Asp-286.
841282	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1653 as residues: Leu-3 to Lys-8.
841283	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1654 as residues: Tyr-1 to Glu-9, Ala-12 to Ser-18, His-63 to Phe-77, Asn-98 to Arg-110.
841286	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1655 as residues: Ser-13 to Arg-19, Leu-28 to Val-35, Pro-37 to Gly-57, Ser-81 to Pro-87, Ile-102 to Arg-111.
841287	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1656 as residues: Arg-1 to Ala-10, Val-23 to Phe-42, Asp-60 to Tyr-69, Pro-71 to Ser-79.
841288	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1657 as residues: Ser-4 to Pro-9, Arg-18 to Pro-26.
841291	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1658 as residues: Lys-16 to Ser-23, Gln-56 to Asp-63, Lys-137 to His-145, Glu-149 to His-156, Glu-163 to Gly-171, Pro-173 to Ala-180, Lys-189 to Ala-206, Glu-208 to Gln-214, Pro-231 to Ser-240.
841294	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1660 as residues: Gly-6 to Gly-12, Glu-19 to Pro-37, Gly-43 to Pro-55, Asp-62 to Gln-78, Arg-89 to Gln-95, Lys-99 to Arg-118, Glu-123 to Ala-139.
841301	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1663 as residues: Asn-8 to Arg-13, Gly-36 to Leu-43, Arg-53 to Cys-59.
841303	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1664 as residues: Pro-23 to Gly-35, Pro-38 to Phe-45, Pro-47 to Gly-56, Val-68 to Tyr-73, Gly-123 to Gly-135, Met-150 to Gln-164, Arg-212 to Ile-220, Arg-284 to Ile-289, Tyr-296 to His-315, Gln-325 to Ile-334, Thr-471 to Arg-476.
841304	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1665 as residues: Phe-33 to Arg-47, Asn-65 to Gly-71, Asp-95 to Gly-100, Asp-152 to Asn-163, His-223 to Gly-229.
841305	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1666 as residues: Gly-5 to Trp-19, Pro-21 to Ser-35, Pro-42 to Ser-58, Pro-64 to Asp-75.
841309	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1667 as residues: Lys-1 to Lys-6, Lys-18 to Asp-25, Thr-46 to Arg-64, His-97 to Lys-105, Glu-113 to Ala-118, Asn-126 to Gly-137, Thr-142 to Pro-147, Glu-155 to Ile-173, Ala-175 to Asn-184, Ser-188 to Glu-222, Glu-228 to Ala-242, Ala-263 to Asp-272, Thr-277 to Asp-288, Lys-293 to Met-308, Ile-348 to Gly-359, Pro-361 to Thr-386, Pro-403 to Arg-411, Asp-466 to Gln-473, Arg-479 to Thr-493, Lys-507 to Lys-513.
841314	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1668 as residues: Leu-4 to Ala-11, Phe-106 to Trp-112, Lys-204 to Ile-209, Ser-224 to Leu-236, Pro-254 to Ser-262, Phe-282 to Met-295.
841316	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1669 as residues: Pro-60 to Ser-67, Lys-86 to Ile-92, Arg-125 to Lys-130, Glu-155 to Asp-161, Glu-170 to Ser-176, Thr-181 to Val-187, Leu-198 to Asn-203, Gln-258 to Lys-263, Pro-271 to Asn-276, Phe-286 to Glu-292.
841318	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1670 as residues: Pro-14 to Trp-25, His-36 to Arg-41, Gly-66 to Tyr-73, Glu-82 to Pro-89.
841321	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1671 as residues: Asp-11 to Gly-19, Asp-26 to Val-31, Ala-52 to Asn-71, Gly-75 to Gly-81, Pro-88 to Gly-119, Pro-125 to Pro-180, Gly-187 to Gly-193, Tyr-196 to Tyr-218.
841324	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1672 as

	residues: Gly-45 to Val-54, Trp-67 to Gly-75, Asp-82 to Asn-90, Ala-124 to Trp-132, Thr-139 to Gln-145.
841326	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1673 as residues: Thr-45 to Asn-50, Lys-60 to Arg-73, Arg-81 to Asp-87, Lys-91 to Ser-96, Pro-105 to Gly-114, Ser-130 to Leu-136, Leu-145 to Ile-154, Cys-279 to Pro-284, Thr-321 to Glu-326, Pro-389 to Thr-398, Ala-406 to Ile-412, Ala-431 to Glu-438, Lys-495 to Glu-500, Asn-520 to Val-526, Glu-541 to Asn-547, Thr-552 to Tyr-557.
841328	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1674 as residues: Asn-64 to Ala-78, Ser-155 to Ala-169, Lys-290 to Asp-314.
841329	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1675 as residues: Leu-10 to Trp-18, Arg-21 to Leu-32, Pro-35 to Leu-55, Arg-74 to Phe-90, Pro-106 to Trp-115, Val-142 to Thr-152.
841330	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1676 as residues: Gly-14 to Ala-19, Arg-34 to Arg-41.
841333	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1677 as residues: Leu-20 to Val-26.
841335	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1679 as residues: Asn-10 to Cys-17.
841336	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1680 as residues: Lys-1 to Arg-9, Ala-57 to Met-66, Ile-70 to Glu-78, Ile-104 to Gly-125, Thr-155 to Glu-160, Pro-174 to Leu-184, Ala-200 to Arg-206, Ser-231 to Ser-255, Gln-281 to Asp-287.
841337	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1681 as residues: Arg-79 to Val-86, Ala-111 to Glu-125, Pro-148 to Met-153, Arg-180 to Leu-188, Pro-275 to Gly-296, Pro-336 to Phe-350, Gly-353 to Ser-362, Val-364 to Arg-371.
841340	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1683 as residues: Pro-39 to Ser-46.
841341	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1684 as residues: Pro-9 to Gly-23, Glu-43 to Ala-51, Ser-62 to Gly-91.
841343	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1686 as residues: Lys-49 to Gly-66, Ala-78 to Ser-85, Gly-90 to Thr-97, Arg-124 to Gly-129.
841352	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1688 as residues: Arg-37 to Leu-47, Gln-93 to Asp-112, Arg-114 to Arg-119, Arg-124 to Arg-142.
841353	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1689 as residues: Leu-23 to Thr-28, Ile-47 to Lys-56, Arg-91 to Gln-99, Gly-111 to Ser-119.
841354	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1690 as residues: Ser-36 to Arg-42.
841360	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1691 as residues: Asn-1 to Thr-11, Pro-64 to Phe-75, Phe-117 to Ile-122, Glu-124 to Arg-131, Trp-142 to Gln-147, Thr-176 to Ser-185, Arg-208 to Gly-215, Gln-238 to Ser-244, Ala-246 to Val-256, Ser-264 to Lys-272.
841405	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1693 as residues: Leu-1 to Gly-14, Arg-21 to Gln-26, Lys-62 to Val-73, His-131 to Asp-136, Glu-142 to Tyr-158, Val-162 to Gly-169, Gln-183 to Gly-189, Glu-205 to Gly-210, Gln-222 to Asp-231, Gly-237 to Tyr-244, Ala-251 to Leu-267, Asp-298 to Asn-305, Glu-332 to Lys-337, Arg-344 to Ala-349.
841526	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1694 as residues: Pro-1 to Arg-8.
841712	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1695 as residues: Gln-34 to Lys-44, Ser-70 to Leu-75, Ala-79 to Pro-89, Glu-94 to Thr-101, Gln-103 to Ser-112.
842042	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1697 as residues: Arg-64 to Glu-69, Ile-78 to Tyr-86, Asp-128 to Gly-148, Pro-166 to Pro-187, Ala-194 to Lys-239, Ala-243 to Ala-255.
842453	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1698 as residues: Gly-41 to Gly-53, Gly-65 to Arg-74.

842635	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1699 as residues: Cys-2 to Asp-11, Lys-39 to Phe-55, Tyr-72 to Trp-78, Thr-154 to Lys-164, Ser-191 to Lys-203, Asp-218 to Asp-223.
842927	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1700 as residues: Pro-8 to Trp-14, Gly-33 to Glu-48, Arg-58 to Lys-67, Thr-76 to Gln-96, Ala-98 to Ser-118, Cys-193 to Thr-201, Leu-225 to Trp-232, Asp-256 to Phe-262.
843237	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1703 as residues: His-1 to Gly-14, Leu-36 to Ser-41, Gln-45 to Arg-59, Gly-66 to Arg-91, Lys-104 to Trp-113, Arg-143 to Leu-148, Val-172 to Val-181, Pro-235 to Lys-242.
843381	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1704 as residues: Arg-9 to Arg-14, Gly-27 to Cys-32, Ser-53 to Leu-61, Ala-66 to Phe-71.
843823	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1706 as residues: Asp-11 to Tyr-16.
844056	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1707 as residues: Lys-145 to Thr-159, Ser-167 to Lys-176, Asn-216 to Lys-224.
844344	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1709 as residues: Gly-4 to Asp-9, Glu-23 to Lys-31, Asn-38 to Tyr-47.
844368	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1710 as residues: His-5 to Gly-15, Pro-97 to Cys-103.
844408	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1711 as residues: Thr-49 to Gln-60.
844867	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1713 as residues: Ile-49 to Thr-60.
845281	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1715 as residues: Gly-5 to Arg-12.
845288	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1716 as residues: Ala-1 to Gly-6, Ala-8 to Val-15, Ala-159 to Pro-164.
845750	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1717 as residues: Arg-1 to Thr-9.
845809	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1718 as residues: Glu-9 to Arg-14, Thr-19 to Arg-27, Asp-48 to Ile-57, Gln-63 to Leu-75, Cys-89 to Thr-104, Gly-106 to Pro-113, Gly-127 to Thr-133, Arg-144 to Asn-157, Ile-179 to Arg-199.
846077	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1719 as residues: Pro-11 to Trp-18, Cys-59 to Pro-68, Thr-77 to Glu-86, Arg-94 to Asn-102.
HPRTI05R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1721 as residues: Pro-22 to Tyr-34.
HPDED94R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1724 as residues: Gly-1 to Glu-6.
HDTGH11R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1725 as residues: Thr-32 to Met-37.
HTEJR60R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1726 as residues: Ala-1 to Ser-6.
HAGGY86R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1727 as residues: Leu-25 to Trp-40, Val-49 to His-56, Leu-60 to Asn-67.
HPIAU47R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1728 as residues: Glu-88 to Leu-93.
HCGAD89R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1729 as residues: Glu-30 to Asp-45.
HAPOD39R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1730 as residues: Tyr-21 to Ala-28, Ser-74 to Gly-81.
HDRAA14R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1733 as residues: Ala-1 to Pro-8, Ala-10 to Val-16, Pro-43 to Leu-52.
HSLCA48R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1734 as residues: Gln-26 to Leu-31.
HMQDF20R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1736 as residues: Phe-33 to Ala-43, His-86 to Ser-93.

HCHOH06R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1737 as residues: Gly-4 to Lys-10, Arg-17 to Glu-24, Gln-36 to Glu-41, Arg-61 to Arg-76.
HLDRN91R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1740 as residues: Arg-22 to Gln-27, Ser-33 to Val-38, Lys-46 to Gly-57, Gln-92 to Gly-97.
HE6GO78R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1743 as residues: Ser-3 to Trp-12.
HSYBY17R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1745 as residues: Gln-30 to Pro-36.
HPJCS07R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1746 as residues: Tyr-25 to Phe-32.
HFKFH08R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1748 as residues: Arg-2 to Gln-8, Val-49 to Asn-54, Gln-58 to Tyr-64.
HPIBI27R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1750 as residues: Glu-17 to Asp-22, Pro-46 to Arg-52, Pro-75 to Asp-84.
HSKJG37R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1751 as residues: Leu-66 to Gly-72, Asp-89 to Pro-97, Thr-104 to Leu-110.
H2LAZ24R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1752 as residues: Pro-20 to Ala-26, Ser-107 to Ala-113, Asp-129 to Gly-135, Thr-139 to Asp-146, Ser-152 to Arg-168, Glu-173 to Pro-180.
H2LAS11R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1756 as residues: Pro-20 to Ser-25, Lys-67 to Phe-76, Pro-78 to Asn-86, Asp-100 to Gly-108, Arg-116 to Gly-122, Glu-153 to Ala-158.
HADMC73R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1758 as residues: Ala-1 to Tyr-9.
HDTDX66R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1760 as residues: Met-2 to Leu-9, Lys-11 to Pro-28, Asp-57 to Leu-68, Gln-81 to Ser-96, Ser-98 to Arg-106.
HLPBB39R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1761 as residues: Cys-27 to Lys-33, Thr-35 to Cys-41.
HKABU38R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1763 as residues: Pro-1 to Pro-11, Ala-17 to Lys-25, Asp-54 to Leu-59, Thr-66 to Arg-76, Arg-90 to Pro-107, Pro-139 to Glu-146.
HATAI03R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1765 as residues: Phe-1 to Asn-6.
HCEDE25R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1766 as residues: Ala-6 to Thr-13.
H2LAO77R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1770 as residues: Ala-16 to Pro-30, Thr-44 to Val-57, Lys-75 to Gly-80, Asp-92 to Leu-102, Ala-113 to Tyr-120.
HNTRW15R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1771 as residues: Met-3 to Lys-9, Ala-16 to Trp-37.
HULBL38R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1773 as residues: Cys-1 to Glu-6, Asp-52 to Asp-65, Lys-82 to Pro-88.
HNTBK49R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1774 as residues: Pro-40 to Gly-45.
HBAFS48R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1775 as residues: Pro-1 to Glu-18, Pro-37 to Met-44.
HOHBU75R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1777 as residues: His-24 to Gly-29, Glu-32 to Asp-37, Gly-47 to Pro-60.
HSLBA61R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1779 as residues: Asn-37 to Thr-42.
HKAKR61R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1782 as residues: Arg-1 to Thr-7.
H2LAD40R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1785 as residues: Trp-13 to Asp-19, Cys-29 to Gln-34, Ala-41 to Arg-52, Gly-54 to Gln-59, Arg-69 to Pro-78.

H2MBU27R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1788 as residues: Asp-3 to Lys-9, Arg-88 to Gln-95.
HDSAH53R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1789 as residues: Asp-7 to Lys-13.
HAIDF69R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1790 as residues: Gln-13 to Pro-22.
HTWJC11R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1793 as residues: Pro-27 to Val-32.
HKAEC40R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1794 as residues: Lys-86 to Lys-91.
HCFNM70R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1795 as residues: Thr-19 to Lys-24.
HKBAB93R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1796 as residues: Lys-9 to Tyr-26, Arg-48 to Lys-53, Ser-68 to Thr-75, Ala-84 to Leu-89.
HMAEA94R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1800 as residues: His-60 to Asp-69, Phe-87 to Ala-93.
HMWEA08R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1801 as residues: Met-3 to Thr-8, Tyr-33 to Gly-38, Lys-54 to Glu-65.
HRACC09R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1803 as residues: Lys-7 to Trp-18.
HOEEC67R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1804 as residues: Lys-24 to Glu-31.
HPFEA40R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1805 as residues: Arg-4 to Ile-20.
HHECI89R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1807 as residues: Ala-1 to Arg-12, Pro-22 to Met-28, Glu-53 to Thr-61, Gly-90 to Ile-97.
HSDFV03R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1808 as residues: Ser-18 to Phe-24, Pro-40 to Thr-46.
HTXPN01R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1809 as residues: Lys-19 to Glu-28.
HACBH95R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1813 as residues: Pro-43 to Gly-51.
HACBY16R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1814 as residues: Arg-1 to Glu-16.
HAHAD34R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1816 as residues: Gly-13 to Ala-21.
HAJAN69R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1817 as residues: Gly-1 to Gly-22, Pro-61 to Ala-70.
HAPPR17R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1819 as residues: Asn-8 to Met-13, Asp-15 to Met-21.
HBGBE20R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1824 as residues: Arg-28 to Leu-33.
HBMVT43R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1828 as residues: Pro-1 to Asn-8.
HCFLN25R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1830 as residues: Gly-16 to Trp-21, Pro-24 to Leu-32.
HCQAW59R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1831 as residues: Gly-1 to Gly-8, Pro-11 to Asn-21.
HDPMA46R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1832 as residues: Glu-14 to Gly-32, Pro-61 to Gly-66.
HDTAQ26R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1833 as residues: Ser-1 to Gly-7.
HDTLD39R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1835 as residues: Thr-14 to Ser-44.
HE2PO63R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1836 as residues: Phe-11 to Lys-17, Gly-36 to Gly-43.

HELHK95R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1838 as residues: Pro-20 to Pro-28.
HETIB72R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1840 as residues: Gln-1 to Glu-9.
HFIYH65R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1842 as residues: Ala-2 to His-8, Gly-26 to Cys-32.
HKIXO47R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1848 as residues: Ala-1 to Arg-8, Val-12 to Lys-25.
HLWBC80R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1851 as residues: Arg-72 to Gly-80, Leu-86 to Phe-92.
HLYAV50R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1852 as residues: Asp-1 to Gly-6, Gly-44 to Arg-50.
HMEKY67R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1853 as residues: Arg-12 to Phe-24, Pro-32 to Ser-43.
HOUDQ92R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1858 as residues: Arg-1 to Cys-7.
HPIAF72R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1860 as residues: Gln-1 to Arg-17, Ala-25 to Pro-32.
HPIAU01R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1861 as residues: Pro-9 to Gly-18.
HPIAU73R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1862 as residues: Arg-9 to Gln-35, Arg-51 to Gly-56.
HPIAW19R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1863 as residues: Ala-16 to Arg-26, Thr-67 to Asn-76.
HPIAZ19R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1864 as residues: Glu-1 to His-6, Gly-19 to Trp-31.
HPIBA31R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1865 as residues: Glu-1 to His-6, Gly-19 to Trp-31.
HPIBS06R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1866 as residues: Pro-25 to Lys-31.
HPICB65R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1867 as residues: Ser-2 to Gln-10, Val-26 to Lys-34, Asp-52 to Glu-58, Arg-93 to Trp-102.
HPJBF22R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1868 as residues: Glu-1 to His-6, Gly-19 to Trp-31.
HPJBZ81R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1869 as residues: Ser-18 to Gly-23.
HSDJK57R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1873 as residues: Thr-53 to Arg-64.
HSIFY54R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1874 as residues: Phe-35 to Asp-58, Phe-92 to Phe-105.
HUFAT72R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1878 as residues: Pro-16 to Phe-25.
HULAI70R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1879 as residues: Pro-13 to Gly-22, Arg-45 to Cys-50.
HTGFW12R	Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 1880 as residues: Pro-6 to Gly-16, Arg-24 to Pro-32.

[0100] The present invention encompasses polypeptides comprising, or alternatively consisting of, an epitope of the polypeptide sequence shown in SEQ ID NO:Y, or an epitope of the polypeptide sequence encoded by the cDNA in the related cDNA clone contained in a deposited library or encoded by a polynucleotide that hybridizes to the complement of an epitope encoding sequence of SEQ ID NO:X, or an epitope encoding sequence contained in the deposited cDNA clone under stringent hybridization conditions, or alternatively, under lower stringency hybridization conditions, as defined supra. The present invention further encompasses polynucleotide sequences encoding an epitope of a polypeptide sequence of the invention (such as, for example, the sequence disclosed in SEQ ID NO:X), polynucleotide sequences of the complementary strand of a polynucleotide sequence encoding an epitope of the invention, and polynucleotide sequences which hybridize to this complementary strand under stringent hybridization conditions or alternatively, under lower stringency hybridization conditions, as defined supra.

[0101] The term "epitopes," as used herein, refers to portions of a polypeptide having antigenic or immunogenic activity in an animal, preferably a mammal, and most preferably in a human. In a preferred embodiment, the present invention encompasses a polypeptide comprising an epitope, as well as the polynucleotide encoding this polypeptide. An "immunogenic epitope," as used herein, is defined as a portion of a protein that elicits an antibody response in an animal, as determined by any method known in the art, for example, by the methods for generating antibodies described infra. (See, for example, Geysen et al., Proc. Natl. Acad. Sci. USA 81:3998- 4002 (1983)). The term "antigenic epitope," as used herein, is defined as a portion of a protein to which an antibody can immunospecifically bind its antigen as determined by any method well known in the art, for example, by the immunoassays described herein. Immunospecific binding excludes non-specific binding but does not necessarily exclude cross- reactivity with other antigens. Antigenic epitopes need not necessarily be immunogenic.

[0102] Fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, R. A., Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985) further described in U.S. Patent No. 4,631,211.)

[0103] In the present invention, antigenic epitopes preferably contain a sequence of at least 4, at least 5, at least 6, at least 7, more preferably at least 8, at least 9, at least

10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 40, at least 50, and, most preferably, between about 15 to about 30 amino acids. Preferred polypeptides comprising immunogenic or antigenic epitopes are at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acid residues in length. Additional non-exclusive preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as portions thereof. Antigenic epitopes are useful, for example, to raise antibodies, including monoclonal antibodies, that specifically bind the epitope. Preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these antigenic epitopes. Antigenic epitopes can be used as the target molecules in immunoassays. (See, for instance, Wilson et al., Cell 37:767-778 (1984); Sutcliffe et al., Science 219:660-666 (1983)).

[0104] Similarly, immunogenic epitopes can be used, for example, to induce antibodies according to methods well known in the art. (See, for instance, Sutcliffe et al., supra; Wilson et al., supra; Chow et al., Proc. Natl. Acad. Sci. USA 82:910-914; and Bittle et al., J. Gen. Virol. 66:2347-2354 (1985). Preferred immunogenic epitopes include the immunogenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these immunogenic epitopes. The polypeptides comprising one or more immunogenic epitopes may be presented for eliciting an antibody response together with a carrier protein, such as an albumin, to an animal system (such as rabbit or mouse), or, if the polypeptide is of sufficient length (at least about 25 amino acids), the polypeptide may be presented without a carrier. However, immunogenic epitopes comprising as few as 8 to 10 amino acids have been shown to be sufficient to raise antibodies capable of binding to, at the very least, linear epitopes in a denatured polypeptide (e.g., in Western blotting).

[0105] Epitope-bearing polypeptides of the present invention may be used to induce antibodies according to methods well known in the art including, but not limited to, in vivo immunization, in vitro immunization, and phage display methods. See, e.g., Sutcliffe et al., supra; Wilson et al., supra, and Bittle et al., J. Gen. Virol., 66:2347-2354 (1985). If in vivo immunization is used, animals may be immunized with free peptide; however, anti-peptide antibody titer may be boosted by coupling the peptide to a macromolecular carrier, such as keyhole limpet hemacyanin (KLH) or tetanus toxoid.

For instance, peptides containing cysteine residues may be coupled to a carrier using a linker such as maleimidobenzoyl- N-hydroxysuccinimide ester (MBS), while other peptides may be coupled to carriers using a more general linking agent such as glutaraldehyde. Animals such as rabbits, rats and mice are immunized with either free or carrier- coupled peptides, for instance, by intraperitoneal and/or intradermal injection of emulsions containing about 100 μg of peptide or carrier protein and Freund's adjuvant or any other adjuvant known for stimulating an immune response. Several booster injections may be needed, for instance, at intervals of about two weeks, to provide a useful titer of anti-peptide antibody which can be detected, for example, by ELISA assay using free peptide adsorbed to a solid surface. The titer of anti-peptide antibodies in serum from an immunized animal may be increased by selection of anti-peptide antibodies, for instance, by adsorption to the peptide on a solid support and elution of the selected antibodies according to methods well known in the art.

[0106] As one of skill in the art will appreciate, and as discussed above, the polypeptides of the present invention , and immunogenic and/or antigenic epitope fragments thereof can be fused to other polypeptide sequences. For example, the polypeptides of the present invention may be fused with the constant domain of immunoglobulins (IgA, IgE, IgG, IgM), or portions thereof (CH1, CH2, CH3, or any combination thereof and portions thereof) resulting in chimeric polypeptides. Such fusion proteins may facilitate purification and may increase half-life in vivo. This has been shown for chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. See, e.g., EP 394,827; Traunecker et al., Nature, 331:84-86 (1988). Enhanced delivery of an antigen across the epithelial barrier to the immune system has been demonstrated for antigens (e.g., insulin) conjugated to an FcRn binding partner such as IgG or Fc fragments (see, e.g., PCT Publications WO 96/22024 and WO 99/04813). IgG Fusion proteins that have a disulfide-linked dimeric structure due to the IgG portion desulfide bonds have also been found to be more efficient in binding and neutralizing other molecules than monomeric polypeptides or fragments thereof alone. See, e.g., Fountoulakis et al., J. Biochem., 270:3958-3964 (1995).

[0107] Similarly, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobulin

molecules together with another human protein or part thereof. In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. (EP-A 0232 262.) Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, may be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See, D. Bennett et al., J. Molecular Recognition 8:52-58 (1995); K. Johanson et al., J. Biol. Chem. 270:9459-9471 (1995).)

[0108] Moreover, the polypeptides of the present invention can be fused to marker sequences, such as a peptide which facilitates purification of the fused polypeptide. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Another peptide tag useful for purification, the "HA" tag, corresponds to an epitope derived from the influenza hemagglutinin protein. (Wilson et al., Cell 37:767 (1984).)

[0109] Thus, any of these above fusions can be engineered using the polynucleotides or the polypeptides of the present invention.

[0110] Nucleic acids encoding the above epitopes can also be recombined with a gene of interest as an epitope tag (e.g., the hemagglutinin ("HA") tag or flag tag) to aid in detection and purification of the expressed polypeptide. For example, a system described by Janknecht et al. allows for the ready purification of non-denatured fusion proteins expressed in human cell lines (Janknecht et al., Proc. Natl. Acad. Sci. USA 88:8972- 897 (1991)). In this system, the gene of interest is subcloned into a vaccinia recombination plasmid such that the open reading frame of the gene is translationally fused to an amino-terminal tag consisting of six histidine residues. The tag serves as a matrix binding domain for the fusion protein. Extracts from cells infected with the recombinant vaccinia virus are loaded onto Ni2+ nitriloacetic acid-agarose column and histidine-tagged proteins can be selectively eluted with imidazole-containing buffers.

[0111] Additional fusion proteins of the invention may be generated through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"). DNA shuffling may be employed to modulate the activities of polypeptides of the invention, such methods can be used to generate polypeptides with altered activity, as well as agonists and antagonists of the polypeptides. See, generally, U.S. Patent Nos. 5,605,793; 5,811,238; 5,830,721; 5,834,252; and 5,837,458, and Patten et al., Curr. Opinion Biotechnol. 8:724-33 (1997); Harayama, Trends Biotechnol. 16(2):76-82 (1998); Hansson, et al., J. Mol. Biol. 287:265-76 (1999); and Lorenzo and Blasco, Biotechniques 24(2):308- 13 (1998) (each of these patents and publications are hereby incorporated by reference in its entirety). In one embodiment, alteration of polynucleotides corresponding to SEQ ID NO:X and the polypeptides encoded by these polynucleotides may be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments by homologous or site-specific recombination to generate variation in the polynucleotide sequence. In another embodiment, polynucleotides of the invention, or the encoded polypeptides, may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of a polynucleotide encoding a polypeptide of the invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules.

[0112] As discussed herein, any polypeptide of the present invention can be used to generate fusion proteins. For example, the polypeptide of the present invention, when fused to a second protein, can be used as an antigenic tag. Antibodies raised against the polypeptide of the present invention can be used to indirectly detect the second protein by binding to the polypeptide. Moreover, because secreted proteins target cellular locations based on trafficking signals, polypeptides of the present invention which are shown to be secreted can be used as targeting molecules once fused to other proteins.

[0113] Examples of domains that can be fused to polypeptides of the present invention include not only heterologous signal sequences, but also other heterologous functional regions. The fusion does not necessarily need to be direct, but may occur through linker sequences.

[0114] In certain preferred embodiments, proteins of the invention comprise fusion proteins wherein the polypeptides are N and/or C- terminal deletion mutants. In preferred embodiments, the application is directed to nucleic acid molecules at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to the nucleic acid sequences encoding polypeptides having the amino acid sequence of the specific N- and C-terminal deletions mutants. Polynucleotides encoding these polypeptides are also encompassed by the invention.

[0115] Moreover, fusion proteins may also be engineered to improve characteristics of the polypeptide of the present invention. For instance, a region of additional amino acids, particularly charged amino acids, may be added to the N-terminus of the polypeptide to improve stability and persistence during purification from the host cell or subsequent handling and storage. Also, peptide moieties may be added to the polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the polypeptide. The addition of peptide moieties to facilitate handling of polypeptides are familiar and routine techniques in the art.

Vectors, Host Cells, and Protein Production

[0116] The present invention also relates to vectors containing the polynucleotide of the present invention, host cells, and the production of polypeptides by recombinant techniques. The vector may be, for example, a phage, plasmid, viral, or retroviral vector. Retroviral vectors may be replication competent or replication defective. In the latter case, viral propagation generally will occur only in complementing host cells.

[0117] The polynucleotides of the invention may be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it may be packaged in vitro using an appropriate packaging cell line and then transduced into host cells.

[0118] The polynucleotide insert should be operatively linked to an appropriate promoter, such as the phage lambda PL promoter, the E. coli lac, trp, phoA and tac promoters, the SV40 early and late promoters and promoters of retroviral LTRs, to name a few. Other suitable promoters will be known to the skilled artisan. The expression constructs will further contain sites for transcription initiation, termination, and, in the

transcribed region, a ribosome binding site for translation. The coding portion of the transcripts expressed by the constructs will preferably include a translation initiating codon at the beginning and a termination codon (UAA, UGA or UAG) appropriately positioned at the end of the polypeptide to be translated.

[0119] As indicated, the expression vectors will preferably include at least one selectable marker. Such markers include dihydrofolate reductase, G418 or neomycin resistance for eukaryotic cell culture and tetracycline, kanamycin or ampicillin resistance genes for culturing in E. coli and other bacteria. Representative examples of appropriate hosts include, but are not limited to, bacterial cells, such as E. coli, Streptomyces and Salmonella typhimurium cells; fungal cells, such as yeast cells (e.g., Saccharomyces cerevisiae or Pichia pastoris (ATCC Accession No. 201178)); insect cells such as Drosophila S2 and Spodoptera Sf9 cells; animal cells such as CHO, COS, 293, and Bowes melanoma cells; and plant cells. Appropriate culture mediums and conditions for the above-described host cells are known in the art.

[0120] Among vectors preferred for use in bacteria include pQE70, pQE60 and pQE-9, available from QIAGEN, Inc.; pBluescript vectors, Phagescript vectors, pNH8A, pNH16a, pNH18A, pNH46A, available from Stratagene Cloning Systems, Inc.; and ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 available from Pharmacia Biotech, Inc. Among preferred eukaryotic vectors are pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; and pSVK3, pBPV, pMSG and pSVL available from Pharmacia. Preferred expression vectors for use in yeast systems include, but are not limited to pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalph, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1, pPIC3.5K, pPIC9K, and PAO815 (all available from Invitrogen, Carlbad, CA). Other suitable vectors will be readily apparent to the skilled artisan.

[0121] Introduction of the construct into the host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection, or other methods. Such methods are described in many standard laboratory manuals, such as Davis et al., Basic Methods In Molecular Biology (1986). It is specifically contemplated that the polypeptides of the present invention may in fact be expressed by a host cell lacking a recombinant vector.

[0122] A polypeptide of this invention can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification.

[0123] Polypeptides of the present invention can also be recovered from: products purified from natural sources, including bodily fluids, tissues and cells, whether directly isolated or cultured; products of chemical synthetic procedures; and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant, insect, and mammalian cells. Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may be glycosylated or may be non-glycosylated. In addition, polypeptides of the invention may also include an initial modified methionine residue, in some cases as a result of host-mediated processes. Thus, it is well known in the art that the N-terminal methionine encoded by the translation initiation codon generally is removed with high efficiency from any protein after translation in all eukaryotic cells. While the N-terminal methionine on most proteins also is efficiently removed in most prokaryotes, for some proteins, this prokaryotic removal process is inefficient, depending on the nature of the amino acid to which the N-terminal methionine is covalently linked.

[0124] In one embodiment, the yeast *Pichia pastoris* is used to express polypeptides of the invention in a eukaryotic system. *Pichia pastoris* is a methylotrophic yeast which can metabolize methanol as its sole carbon source. A main step in the methanol metabolization pathway is the oxidation of methanol to formaldehyde using O_2. This reaction is catalyzed by the enzyme alcohol oxidase. In order to metabolize methanol as its sole carbon source, *Pichia pastoris* must generate high levels of alcohol oxidase due, in part, to the relatively low affinity of alcohol oxidase for O_2. Consequently, in a growth medium depending on methanol as a main carbon source, the promoter region of one of the two alcohol oxidase genes (*AOX1*) is highly active. In the presence of methanol, alcohol oxidase produced from the *AOX1* gene comprises up to approximately 30% of the total soluble protein in *Pichia pastoris*. *See*, Ellis, S.B., *et al.*, *Mol. Cell. Biol.* 5:1111-21

(1985); Koutz, P.J, *et al., Yeast* 5:167-77 (1989); Tschopp, J.F., *et al., Nucl. Acids Res.* 15:3859-76 (1987). Thus, a heterologous coding sequence, such as, for example, a polynucleotide of the present invention, under the transcriptional regulation of all or part of the *AOX1* regulatory sequence is expressed at exceptionally high levels in *Pichia* yeast grown in the presence of methanol.

[0125] In one example, the plasmid vector pPIC9K is used to express DNA encoding a polypeptide of the invention, as set forth herein, in a *Pichea* yeast system essentially as described in "*Pichia* Protocols: Methods in Molecular Biology," D.R. Higgins and J. Cregg, eds. The Humana Press, Totowa, NJ, 1998. This expression vector allows expression and secretion of a polypeptide of the invention by virtue of the strong *AOX1* promoter linked to the *Pichia pastoris* alkaline phosphatase (PHO) secretory signal peptide (i.e., leader) located upstream of a multiple cloning site.

[0126] Many other yeast vectors could be used in place of pPIC9K, such as, pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalpha, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1, pPIC3.5K, and PAO815, as one skilled in the art would readily appreciate, as long as the proposed expression construct provides appropriately located signals for transcription, translation, secretion (if desired), and the like, including an in-frame AUG as required.

[0127] In another embodiment, high-level expression of a heterologous coding sequence, such as, for example, a polynucleotide of the present invention, may be achieved by cloning the heterologous polynucleotide of the invention into an expression vector such as, for example, pGAPZ or pGAPZalpha, and growing the yeast culture in the absence of methanol.

[0128] In addition to encompassing host cells containing the vector constructs discussed herein, the invention also encompasses primary, secondary, and immortalized host cells of vertebrate origin, particularly mammalian origin, that have been engineered to delete or replace endogenous genetic material (e.g., coding sequence), and/or to include genetic material (e.g., heterologous polynucleotide sequences) that is operably associated with polynucleotides of the invention, and which activates, alters, and/or amplifies endogenous polynucleotides. For example, techniques known in the art may be used to operably associate heterologous control regions (e.g., promoter and/or enhancer) and

endogenous polynucleotide sequences via homologous recombination (see, e.g., U.S. Patent No. 5,641,670, issued June 24, 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989), the disclosures of each of which are incorporated by reference in their entireties).

[0129] In addition, polypeptides of the invention can be chemically synthesized using techniques known in the art (e.g., see Creighton, 1983, Proteins: Structures and Molecular Principles, W.H. Freeman & Co., N.Y., and Hunkapiller et al., *Nature*, 310:105-111 (1984)). For example, a polypeptide corresponding to a fragment of a polypeptide can be synthesized by use of a peptide synthesizer. Furthermore, if desired, nonclassical amino acids or chemical amino acid analogs can be introduced as a substitution or addition into the polypeptide sequence. Non-classical amino acids include, but are not limited to, to the D-isomers of the common amino acids, 2,4-diaminobutyric acid, a-amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid, g-Abu, e-Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, homocitrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, b-alanine, fluoro-amino acids, designer amino acids such as b-methyl amino acids, Ca-methyl amino acids, Na-methyl amino acids, and amino acid analogs in general. Furthermore, the amino acid can be D (dextrorotary) or L (levorotary).

[0130] Non-naturally occurring variants may be produced using art-known mutagenesis techniques, which include, but are not limited to oligonucleotide mediated mutagenesis, alanine scanning, PCR mutagenesis, site directed mutagenesis (*see, e.g.*, Carter *et al., Nucl. Acids Res. 13*:4331 (1986); and Zoller *et al., Nucl. Acids Res. 10*:6487 (1982)), cassette mutagenesis (*see, e.g.*, Wells *et al., Gene 34*:315 (1985)), restriction selection mutagenesis (*see, e.g.*, Wells *et al., Philos. Trans. R. Soc. London SerA 317*:415 (1986)).

[0131] The invention additionally, encompasses polypeptides of the present invention which are differentially modified during or after translation, e.g., by glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to an antibody molecule or other

cellular ligand, etc. Any of numerous chemical modifications may be carried out by known techniques, including but not limited, to specific chemical cleavage by cyanogen bromide, trypsin, chymotrypsin, papain, V8 protease, $NaBH_4$; acetylation, formylation, oxidation, reduction; metabolic synthesis in the presence of tunicamycin; etc.

[0132] Additional post-translational modifications encompassed by the invention include, for example, e.g., N-linked or O-linked carbohydrate chains, processing of N-terminal or C-terminal ends), attachment of chemical moieties to the amino acid backbone, chemical modifications of N-linked or O-linked carbohydrate chains, and addition or deletion of an N-terminal methionine residue as a result of procaryotic host cell expression. The polypeptides may also be modified with a detectable label, such as an enzymatic, fluorescent, isotopic or affinity label to allow for detection and isolation of the protein.

[0133] Also provided by the invention are chemically modified derivatives of the polypeptides of the invention which may provide additional advantages such as increased solubility, stability and circulating time of the polypeptide, or decreased immunogenicity (see U.S. Patent No. 4,179,337). The chemical moieties for derivitization may be selected from water soluble polymers such as polyethylene glycol, ethylene glycol/propylene glycol copolymers, carboxymethylcellulose, dextran, polyvinyl alcohol and the like. The polypeptides may be modified at random positions within the molecule, or at predetermined positions within the molecule and may include one, two, three or more attached chemical moieties.

[0134] The polymer may be of any molecular weight, and may be branched or unbranched. For polyethylene glycol, the preferred molecular weight is between about 1 kDa and about 100 kDa (the term "about" indicating that in preparations of polyethylene glycol, some molecules will weigh more, some less, than the stated molecular weight) for ease in handling and manufacturing. Other sizes may be used, depending on the desired therapeutic profile (e.g., the duration of sustained release desired, the effects, if any on biological activity, the ease in handling, the degree or lack of antigenicity and other known effects of the polyethylene glycol to a therapeutic protein or analog). For example, the polyethylene glycol may have an average molecular weight of about 200; 500; 1000; 1500; 2000; 2500; 3000; 3500; 4000; 4500; 5000; 5500; 6000; 6500; 7000; 7500; 8000; 8500; 9000; 9500; 10,000; 10,500; 11,000; 11,500; 12,000; 12,500; 13,000; 13,500;

14,000; 14,500; 15,000; 15,500; 16,000; 16,500; 17,000; 17,500; 18,000; 18,500; 19,000; 19,500; 20,000; 25,000; 30,000; 35,000; 40,000; 50,000; 55,000; 60,000; 65,000; 70,000; 75,000; 80,000; 85,000; 90,000; 95,000; or 100,000 kDa.

[0135] As noted above, the polyethylene glycol may have a branched structure. Branched polyethylene glycols are described, for example, in U.S. Patent No. 5,643,575; Morpurgo *et al., Appl. Biochem. Biotechnol. 56*:59-72 (1996); Vorobjev *et al., Nucleosides Nucleotides 18*:2745-2750 (1999); and Caliceti *et al., Bioconjug. Chem. 10*:638-646 (1999), the disclosures of each of which are incorporated herein by reference.

[0136] The polyethylene glycol molecules (or other chemical moieties) should be attached to the protein with consideration of effects on functional or antigenic domains of the protein. There are a number of attachment methods available to those skilled in the art, e.g., EP 0 401 384, herein incorporated by reference (coupling PEG to G-CSF), see also Malik et al., Exp. Hematol. 20:1028-1035 (1992) (reporting pegylation of GM-CSF using tresyl chloride). For example, polyethylene glycol may be covalently bound through amino acid residues via a reactive group, such as, a free amino or carboxyl group. Reactive groups are those to which an activated polyethylene glycol molecule may be bound. The amino acid residues having a free amino group may include lysine residues and the N-terminal amino acid residues; those having a free carboxyl group may include aspartic acid residues glutamic acid residues and the C-terminal amino acid residue. Sulfhydryl groups may also be used as a reactive group for attaching the polyethylene glycol molecules. Preferred for therapeutic purposes is attachment at an amino group, such as attachment at the N-terminus or lysine group.

[0137] As suggested above, polyethylene glycol may be attached to proteins via linkage to any of a number of amino acid residues. For example, polyethylene glycol can be linked to a proteins via covalent bonds to lysine, histidine, aspartic acid, glutamic acid, or cysteine residues. One or more reaction chemistries may be employed to attach polyethylene glycol to specific amino acid residues (e.g., lysine, histidine, aspartic acid, glutamic acid, or cysteine) of the protein or to more than one type of amino acid residue (e.g., lysine, histidine, aspartic acid, glutamic acid, cysteine and combinations thereof) of the protein.

[0138] One may specifically desire proteins chemically modified at the N-terminus. Using polyethylene glycol as an illustration of the present composition, one

may select from a variety of polyethylene glycol molecules (by molecular weight, branching, etc.), the proportion of polyethylene glycol molecules to protein (polypeptide) molecules in the reaction mix, the type of pegylation reaction to be performed, and the method of obtaining the selected N-terminally pegylated protein. The method of obtaining the N-terminally pegylated preparation (i.e., separating this moiety from other monopegylated moieties if necessary) may be by purification of the N-terminally pegylated material from a population of pegylated protein molecules. Selective proteins chemically modified at the N-terminus modification may be accomplished by reductive alkylation which exploits differential reactivity of different types of primary amino groups (lysine versus the N-terminal) available for derivatization in a particular protein. Under the appropriate reaction conditions, substantially selective derivatization of the protein at the N-terminus with a carbonyl group containing polymer is achieved.

[0139] As indicated above, pegylation of the proteins of the invention may be accomplished by any number of means. For example, polyethylene glycol may be attached to the protein either directly or by an intervening linker. Linkerless systems for attaching polyethylene glycol to proteins are described in Delgado *et al., Crit. Rev. Thera. Drug Carrier Sys. 9*:249-304 (1992); Francis *et al., Intern. J. of Hematol. 68*:1-18 (1998); U.S. Patent No. 4,002,531; U.S. Patent No. 5,349,052; WO 95/06058; and WO 98/32466, the disclosures of each of which are incorporated herein by reference.

[0140] One system for attaching polyethylene glycol directly to amino acid residues of proteins without an intervening linker employs tresylated MPEG, which is produced by the modification of monmethoxy polyethylene glycol (MPEG) using tresylchloride ($ClSO_2CH_2CF_3$). Upon reaction of protein with tresylated MPEG, polyethylene glycol is directly attached to amine groups of the protein. Thus, the invention includes protein-polyethylene glycol conjugates produced by reacting proteins of the invention with a polyethylene glycol molecule having a 2,2,2-trifluoreothane sulphonyl group.

[0141] Polyethylene glycol can also be attached to proteins using a number of different intervening linkers. For example, U.S. Patent No. 5,612,460, the entire disclosure of which is incorporated herein by reference, discloses urethane linkers for connecting polyethylene glycol to proteins. Protein-polyethylene glycol conjugates wherein the polyethylene glycol is attached to the protein by a linker can also be produced

by reaction of proteins with compounds such as MPEG-succinimidylsuccinate, MPEG activated with 1,1'-carbonyldiimidazole, MPEG-2,4,5-trichloropenylcarbonate, MPEG-p-nitrophenolcarbonate, and various MPEG-succinate derivatives. A number additional polyethylene glycol derivatives and reaction chemistries for attaching polyethylene glycol to proteins are described in WO 98/32466, the entire disclosure of which is incorporated herein by reference. Pegylated protein products produced using the reaction chemistries set out herein are included within the scope of the invention.

[0142] The number of polyethylene glycol moieties attached to each protein of the invention (*i.e.*, the degree of substitution) may also vary. For example, the pegylated proteins of the invention may be linked, on average, to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 17, 20, or more polyethylene glycol molecules. Similarly, the average degree of substitution within ranges such as 1-3, 2-4, 3-5, 4-6, 5-7, 6-8, 7-9, 8-10, 9-11, 10-12, 11-13, 12-14, 13-15, 14-16, 15-17, 16-18, 17-19, or 18-20 polyethylene glycol moieties per protein molecule. Methods for determining the degree of substitution are discussed, for example, in Delgado *et al., Crit. Rev. Thera. Drug Carrier Sys. 9*:249-304 (1992).

[0143] The prostate cancer antigen polypeptides of the invention may be in monomers or multimers (i.e., dimers, trimers, tetramers and higher multimers). Accordingly, the present invention relates to monomers and multimers of the polypeptides of the invention, their preparation, and compositions (preferably, Therapeutics) containing them. In specific embodiments, the polypeptides of the invention are monomers, dimers, trimers or tetramers. In additional embodiments, the multimers of the invention are at least dimers, at least trimers, or at least tetramers.

[0144] Multimers encompassed by the invention may be homomers or heteromers. As used herein, the term homomer, refers to a multimer containing only polypeptides corresponding to the amino acid sequence of SEQ ID NO:Y or an amino acid sequence encoded by SEQ ID NO:X, and/or an amino acid sequence encoded by the cDNA in a related cDNA clone contained in a deposited library (including fragments, variants, splice variants, and fusion proteins, corresponding to any one of these as described herein). These homomers may contain polypeptides having identical or different amino acid sequences. In a specific embodiment, a homomer of the invention is a multimer containing only polypeptides having an identical amino acid sequence. In another specific embodiment, a homomer of the invention is a multimer containing polypeptides having

different amino acid sequences. In specific embodiments, the multimer of the invention is a homodimer (e.g., containing polypeptides having identical or different amino acid sequences) or a homotrimer (e.g., containing polypeptides having identical and/or different amino acid sequences). In additional embodiments, the homomeric multimer of the invention is at least a homodimer, at least a homotrimer, or at least a homotetramer.

[0145] As used herein, the term heteromer refers to a multimer containing one or more heterologous polypeptides (i.e., polypeptides of different proteins) in addition to the polypeptides of the invention. In a specific embodiment, the multimer of the invention is a heterodimer, a heterotrimer, or a heterotetramer. In additional embodiments, the heteromeric multimer of the invention is at least a heterodimer, at least a heterotrimer, or at least a heterotetramer.

[0146] Multimers of the invention may be the result of hydrophobic, hydrophilic, ionic and/or covalent associations and/or may be indirectly linked, by for example, liposome formation. Thus, in one embodiment, multimers of the invention, such as, for example, homodimers or homotrimers, are formed when polypeptides of the invention contact one another in solution. In another embodiment, heteromultimers of the invention, such as, for example, heterotrimers or heterotetramers, are formed when polypeptides of the invention contact antibodies to the polypeptides of the invention (including antibodies to the heterologous polypeptide sequence in a fusion protein of the invention) in solution. In other embodiments, multimers of the invention are formed by covalent associations with and/or between the polypeptides of the invention. Such covalent associations may involve one or more amino acid residues contained in the polypeptide sequence (e.g., that recited in SEQ ID NO:Y, or contained in a polypeptide encoded by SEQ ID NO:X, and/or by the cDNA in the related cDNA clone contained in a deposited library). In one instance, the covalent associations are cross-linking between cysteine residues located within the polypeptide sequences which interact in the native (i.e., naturally occurring) polypeptide. In another instance, the covalent associations are the consequence of chemical or recombinant manipulation. Alternatively, such covalent associations may involve one or more amino acid residues contained in the heterologous polypeptide sequence in a fusion protein. In one example, covalent associations are between the heterologous sequence contained in a fusion protein of the invention (see, e.g., US Patent Number 5,478,925). In a specific example, the covalent associations are between the heterologous sequence

contained in a Fc fusion protein of the invention (as described herein). In another specific example, covalent associations of fusion proteins of the invention are between heterologous polypeptide sequence from another protein that is capable of forming covalently associated multimers, such as for example, oseteoprotegerin (see, e.g., International Publication NO: WO 98/49305, the contents of which are herein incorporated by reference in its entirety). In another embodiment, two or more polypeptides of the invention are joined through peptide linkers. Examples include those peptide linkers described in U.S. Pat. No. 5,073,627 (hereby incorporated by reference). Proteins comprising multiple polypeptides of the invention separated by peptide linkers may be produced using conventional recombinant DNA technology.

[0147] Another method for preparing multimer polypeptides of the invention involves use of polypeptides of the invention fused to a leucine zipper or isoleucine zipper polypeptide sequence. Leucine zipper and isoleucine zipper domains are polypeptides that promote multimerization of the proteins in which they are found. Leucine zippers were originally identified in several DNA-binding proteins (Landschulz et al., Science 240:1759, (1988)), and have since been found in a variety of different proteins. Among the known leucine zippers are naturally occurring peptides and derivatives thereof that dimerize or trimerize. Examples of leucine zipper domains suitable for producing soluble multimeric proteins of the invention are those described in PCT application WO 94/10308, hereby incorporated by reference. Recombinant fusion proteins comprising a polypeptide of the invention fused to a polypeptide sequence that dimerizes or trimerizes in solution are expressed in suitable host cells, and the resulting soluble multimeric fusion protein is recovered from the culture supernatant using techniques known in the art.

[0148] Trimeric polypeptides of the invention may offer the advantage of enhanced biological activity. Preferred leucine zipper moieties and isoleucine moieties are those that preferentially form trimers. One example is a leucine zipper derived from lung surfactant protein D (SPD), as described in Hoppe et al. (FEBS Letters 344:191, (1994)) and in U.S. patent application Ser. No. 08/446,922, hereby incorporated by reference. Other peptides derived from naturally occurring trimeric proteins may be employed in preparing trimeric polypeptides of the invention.

[0149] In another example, proteins of the invention are associated by interactions between Flag® polypeptide sequence contained in fusion proteins of the invention

containing Flag® polypeptide seuqence. In a further embodiment, associations proteins of the invention are associated by interactions between heterologous polypeptide sequence contained in Flag® fusion proteins of the invention and anti-Flag® antibody.

[0150] The multimers of the invention may be generated using chemical techniques known in the art. For example, polypeptides desired to be contained in the multimers of the invention may be chemically cross-linked using linker molecules and linker molecule length optimization techniques known in the art (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Additionally, multimers of the invention may be generated using techniques known in the art to form one or more inter-molecule cross-links between the cysteine residues located within the sequence of the polypeptides desired to be contained in the multimer (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Further, polypeptides of the invention may be routinely modified by the addition of cysteine or biotin to the C-terminus or N-terminus of the polypeptide and techniques known in the art may be applied to generate multimers containing one or more of these modified polypeptides (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Additionally, techniques known in the art may be applied to generate liposomes containing the polypeptide components desired to be contained in the multimer of the invention (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety).

[0151] Alternatively, multimers of the invention may be generated using genetic engineering techniques known in the art. In one embodiment, polypeptides contained in multimers of the invention are produced recombinantly using fusion protein technology described herein or otherwise known in the art (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). In a specific embodiment, polynucleotides coding for a homodimer of the invention are generated by ligating a polynucleotide sequence encoding a polypeptide of the invention to a sequence encoding a linker polypeptide and then further to a synthetic polynucleotide encoding the translated product of the polypeptide in the reverse orientation from the original C-terminus to the N-terminus (lacking the leader sequence) (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). In another embodiment, recombinant techniques described herein or otherwise known in the art are applied to generate

recombinant polypeptides of the invention which contain a transmembrane domain (or hyrophobic or signal peptide) and which can be incorporated by membrane reconstitution techniques into liposomes (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety).

Antibodies

[0152] Further polypeptides of the invention relate to antibodies and T-cell antigen receptors (TCR) which immunospecifically bind a polypeptide, polypeptide fragment, or variant of SEQ ID NO:Y, and/or an epitope, of the present invention (as determined by immunoassays well known in the art for assaying specific antibody-antigen binding). Antibodies of the invention include, but are not limited to, polyclonal, monoclonal, multispecific, human, humanized or chimeric antibodies, single chain antibodies, Fab fragments, F(ab') fragments, fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies (including, e.g., anti-Id antibodies to antibodies of the invention), and epitope-binding fragments of any of the above. The term "antibody," as used herein, refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e., molecules that contain an antigen binding site that immunospecifically binds an antigen. The immunoglobulin molecules of the invention can be of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule.

[0153] Most preferably the antibodies are human antigen-binding antibody fragments of the present invention and include, but are not limited to, Fab, Fab' and F(ab')2, Fd, single-chain Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (sdFv) and fragments comprising either a VL or VH domain. Antigen-binding antibody fragments, including single-chain antibodies, may comprise the variable region(s) alone or in combination with the entirety or a portion of the following: hinge region, CH1, CH2, and CH3 domains. Also included in the invention are antigen-binding fragments also comprising any combination of variable region(s) with a hinge region, CH1, CH2, and CH3 domains. The antibodies of the invention may be from any animal origin including birds and mammals. Preferably, the antibodies are human, murine (e.g., mouse and rat), donkey, ship rabbit, goat, guinea pig, camel, horse, or chicken. As used herein, "human" antibodies include antibodies having the amino acid sequence of a human immunoglobulin

and include antibodies isolated from human immunoglobulin libraries or from animals transgenic for one or more human immunoglobulin and that do not express endogenous immunoglobulins, as described infra and, for example in, U.S. Patent No. 5,939,598 by Kucherlapati et al.

[0154] The antibodies of the present invention may be monospecific, bispecific, trispecific or of greater multispecificity. Multispecific antibodies may be specific for different epitopes of a polypeptide of the present invention or may be specific for both a polypeptide of the present invention as well as for a heterologous epitope, such as a heterologous polypeptide or solid support material. See, e.g., PCT publications WO 93/17715; WO 92/08802; WO 91/00360; WO 92/05793; Tutt, et al., J. Immunol. 147:60-69 (1991); U.S. Patent Nos. 4,474,893; 4,714,681; 4,925,648; 5,573,920; 5,601,819; Kostelny et al., J. Immunol. 148:1547-1553 (1992).

[0155] Antibodies of the present invention may be described or specified in terms of the epitope(s) or portion(s) of a polypeptide of the present invention which they recognize or specifically bind. The epitope(s) or polypeptide portion(s) may be specified as described herein, e.g., by N-terminal and C-terminal positions, or by size in contiguous amino acid residues. Antibodies which specifically bind any epitope or polypeptide of the present invention may also be excluded. Therefore, the present invention includes antibodies that specifically bind polypeptides of the present invention, and allows for the exclusion of the same.

[0156] Antibodies of the present invention may also be described or specified in terms of their cross-reactivity. Antibodies that do not bind any other analog, ortholog, or homolog of a polypeptide of the present invention are included. Antibodies that bind polypeptides with at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55%, and at least 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In specific embodiments, antibodies of the present invention cross-react with murine, rat and/or rabbit homologs of human proteins and the corresponding epitopes thereof. Antibodies that do not bind polypeptides with less than 95%, less than 90%, less than 85%, less than 80%, less than 75%, less than 70%, less than 65%, less than 60%, less than 55%, and less than 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the

present invention are also included in the present invention. In a specific embodiment, the above-described cross-reactivity is with respect to any single specific antigenic or immunogenic polypeptide, or combination(s) of 2, 3, 4, 5, or more of the specific antigenic and/or immunogenic polypeptides disclosed herein. Further included in the present invention are antibodies which bind polypeptides encoded by polynucleotides which hybridize to a polynucleotide of the present invention under stringent hybridization conditions (as described herein). Antibodies of the present invention may also be described or specified in terms of their binding affinity to a polypeptide of the invention. Preferred binding affinities include those with a dissociation constant or Kd less than 5 X 10^{-2} M, 10^{-2} M, 5 X 10^{-3} M, 10^{-3} M, 5 X 10^{-4} M, 10^{-4} M, 5 X 10^{-5} M, 10^{-5} M, 5 X 10^{-6} M, 10^{-6}M, 5 X 10^{-7} M, 10^{7} M, 5 X 10^{-8} M, 10^{-8} M, 5 X 10^{-9} M, 10^{-9} M, 5 X 10^{-10} M, 10^{-10} M, 5 X 10^{-11} M, 10^{-11} M, 5 X 10^{-12} M, $^{10-12}$ M, 5 X 10^{-13} M, 10^{-13} M, 5 X 10^{-14} M, 10^{-14} M, 5 X 10^{-15} M, or $^{10-15}$ M.

[0157] The invention also provides antibodies that competitively inhibit binding of an antibody to an epitope of the invention as determined by any method known in the art for determining competitive binding, for example, the immunoassays described herein. In preferred embodiments, the antibody competitively inhibits binding to the epitope by at least 95%, at least 90%, at least 85 %, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50%.

[0158] Antibodies of the present invention may act as agonists or antagonists of the polypeptides of the present invention. For example, the present invention includes antibodies which disrupt the receptor/ligand interactions with the polypeptides of the invention either partially or fully. Preferrably, antibodies of the present invention bind an antigenic epitope disclosed herein, or a portion thereof. The invention features both receptor-specific antibodies and ligand-specific antibodies. The invention also features receptor-specific antibodies which do not prevent ligand binding but prevent receptor activation. Receptor activation (i.e., signaling) may be determined by techniques described herein or otherwise known in the art. For example, receptor activation can be determined by detecting the phosphorylation (e.g., tyrosine or serine/threonine) of the receptor or its substrate by immunoprecipitation followed by western blot analysis (for example, as described supra). In specific embodiments, antibodies are provided that inhibit ligand activity or receptor activity by at least 95%, at least 90%, at least 85%, at

least 80%, at least 75%, at least 70%, at least 60%, or at least 50% of the activity in absence of the antibody.

[0159] The invention also features receptor-specific antibodies which both prevent ligand binding and receptor activation as well as antibodies that recognize the receptor-ligand complex, and, preferably, do not specifically recognize the unbound receptor or the unbound ligand. Likewise, included in the invention are neutralizing antibodies which bind the ligand and prevent binding of the ligand to the receptor, as well as antibodies which bind the ligand, thereby preventing receptor activation, but do not prevent the ligand from binding the receptor. Further included in the invention are antibodies which activate the receptor. These antibodies may act as receptor agonists, i.e., potentiate or activate either all or a subset of the biological activities of the ligand-mediated receptor activation, for example, by inducing dimerization of the receptor. The antibodies may be specified as agonists, antagonists or inverse agonists for biological activities comprising the specific biological activities of the peptides of the invention disclosed herein. The above antibody agonists can be made using methods known in the art. See, e.g., PCT publication WO 96/40281; U.S. Patent No. 5,811,097; Deng et al., Blood 92(6):1981-1988 (1998); Chen et al., Cancer Res. 58(16):3668-3678 (1998); Harrop et al., J. Immunol. 161(4):1786-1794 (1998); Zhu et al., Cancer Res. 58(15):3209-3214 (1998); Yoon et al., J. Immunol. 160(7):3170-3179 (1998); Prat et al., J. Cell. Sci. 111(Pt2):237-247 (1998); Pitard et al., J. Immunol. Methods 205(2):177-190 (1997); Liautard et al., Cytokine 9(4):233-241 (1997); Carlson et al., J. Biol. Chem. 272(17):11295-11301 (1997); Taryman et al., Neuron 14(4):755-762 (1995); Muller et al., Structure 6(9):1153-1167 (1998); Bartunek et al., Cytokine 8(1):14-20 (1996) (which are all incorporated by reference herein in their entireties).

[0160] Antibodies of the present invention may be used, for example, but not limited to, to purify, detect, and target the polypeptides of the present invention, including both in vitro and in vivo diagnostic and therapeutic methods. For example, the antibodies have use in immunoassays for qualitatively and quantitatively measuring levels of the polypeptides of the present invention in biological samples. See, e.g., Harlow et al., Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988) (incorporated by reference herein in its entirety).

[0161] As discussed in more detail below, the antibodies of the present invention may be used either alone or in combination with other compositions. The antibodies may further be recombinantly fused to a heterologous polypeptide at the N- or C-terminus or chemically conjugated (including covalently and non-covalently conjugations) to polypeptides or other compositions. For example, antibodies of the present invention may be recombinantly fused or conjugated to molecules useful as labels in detection assays and effector molecules such as heterologous polypeptides, drugs, radionuclides, or toxins. See, e.g., PCT publications WO 92/08495; WO 91/14438; WO 89/12624; U.S. Patent No. 5,314,995; and EP 396,387.

[0162] The antibodies of the invention include derivatives that are modified, i.e, by the covalent attachment of any type of molecule to the antibody such that covalent attachment does not prevent the antibody from generating an anti-idiotypic response. For example, but not by way of limitation, the antibody derivatives include antibodies that have been modified, e.g., by glycosylation, acetylation, pegylation, phosphylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of numerous chemical modifications may be carried out by known techniques, including, but not limited to specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Additionally, the derivative may contain one or more non-classical amino acids.

[0163] The antibodies of the present invention may be generated by any suitable method known in the art. Polyclonal antibodies to an antigen-of- interest can be produced by various procedures well known in the art. For example, a polypeptide of the invention can be administered to various host animals including, but not limited to, rabbits, mice, rats, etc. to induce the production of sera containing polyclonal antibodies specific for the antigen. Various adjuvants may be used to increase the immunological response, depending on the host species, and include but are not limited to, Freund's (complete and incomplete), mineral gels such as aluminum hydroxide, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanins, dinitrophenol, and potentially useful human adjuvants such as BCG (bacille Calmette-Guerin) and corynebacterium parvum. Such adjuvants are also well known in the art.

[0164] Monoclonal antibodies can be prepared using a wide variety of techniques known in the art including the use of hybridoma, recombinant, and phage display technologies, or a combination thereof. For example, monoclonal antibodies can be produced using hybridoma techniques including those known in the art and taught, for example, in Harlow et al., Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling, et al., in: Monoclonal Antibodies and T-Cell Hybridomas 563-681 (Elsevier, N.Y., 1981) (said references incorporated by reference in their entireties). The term "monoclonal antibody" as used herein is not limited to antibodies produced through hybridoma technology. The term "monoclonal antibody" refers to an antibody that is derived from a single clone, including any eukaryotic, prokaryotic, or phage clone, and not the method by which it is produced.

[0165] Methods for producing and screening for specific antibodies using hybridoma technology are routine and well known in the art and are discussed in detail in the Examples. In a non-limiting example, mice can be immunized with a polypeptide of the invention or a cell expressing such peptide. Once an immune response is detected, e.g., antibodies specific for the antigen are detected in the mouse serum, the mouse spleen is harvested and splenocytes isolated. The splenocytes are then fused by well known techniques to any suitable myeloma cells, for example cells from cell line SP20 available from the ATCC. Hybridomas are selected and cloned by limited dilution. The hybridoma clones are then assayed by methods known in the art for cells that secrete antibodies capable of binding a polypeptide of the invention. Ascites fluid, which generally contains high levels of antibodies, can be generated by immunizing mice with positive hybridoma clones.

[0166] Accordingly, the present invention provides methods of generating monoclonal antibodies as well as antibodies produced by the method comprising culturing a hybridoma cell secreting an antibody of the invention wherein, preferably, the hybridoma is generated by fusing splenocytes isolated from a mouse immunized with an antigen of the invention with myeloma cells and then screening the hybridomas resulting from the fusion for hybridoma clones that secrete an antibody able to bind a polypeptide of the invention.

[0167] Antibody fragments which recognize specific epitopes may be generated by known techniques. For example, Fab and F(ab')2 fragments of the invention may be

produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')2 fragments). F(ab')2 fragments contain the variable region, the light chain constant region and the CH1 domain of the heavy chain.

[0168] For example, the antibodies of the present invention can also be generated using various phage display methods known in the art. In phage display methods, functional antibody domains are displayed on the surface of phage particles which carry the polynucleotide sequences encoding them. In a particular embodiment, such phage can be utilized to display antigen binding domains expressed from a repertoire or combinatorial antibody library (e.g., human or murine). Phage expressing an antigen binding domain that binds the antigen of interest can be selected or identified with antigen, e.g., using labeled antigen or antigen bound or captured to a solid surface or bead. Phage used in these methods are typically filamentous phage including fd and M13 binding domains expressed from phage with Fab, Fv or disulfide stabilized Fv antibody domains recombinantly fused to either the phage gene III or gene VIII protein. Examples of phage display methods that can be used to make the antibodies of the present invention include those disclosed in Brinkman et al., J. Immunol. Methods 182:41-50 (1995); Ames et al., J. Immunol. Methods 184:177-186 (1995); Kettleborough et al., Eur. J. Immunol. 24:952-958 (1994); Persic et al., Gene 187 9-18 (1997); Burton et al., Advances in Immunology 57:191-280 (1994); PCT application No. PCT/GB91/01134; PCT publications WO 90/02809; WO 91/10737; WO 92/01047; WO 92/18619; WO 93/11236; WO 95/15982; WO 95/20401; and U.S. Patent Nos. 5,698,426; 5,223,409; 5,403,484; 5,580,717; 5,427,908; 5,750,753; 5,821,047; 5,571,698; 5,427,908; 5,516,637; 5,780,225; 5,658,727; 5,733,743 and 5,969,108; each of which is incorporated herein by reference in its entirety.

[0169] As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including human antibodies, or any other desired antigen binding fragment, and expressed in any desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, e.g., as described in detail below. For example, techniques to recombinantly produce Fab, Fab' and F(ab')2 fragments can also be employed using methods known in the art such as those disclosed in PCT publication WO 92/22324; Mullinax et al., BioTechniques 12(6):864-869 (1992); and Sawai et al., AJRI 34:26-34 (1995); and Better

et al., Science 240:1041-1043 (1988) (said references incorporated by reference in their entireties).

[0170] Examples of techniques which can be used to produce single-chain Fvs and antibodies include those described in U.S. Patents 4,946,778 and 5,258,498; Huston et al., Methods in Enzymology 203:46-88 (1991); Shu et al., PNAS 90:7995-7999 (1993); and Skerra et al., Science 240:1038-1040 (1988). For some uses, including in vivo use of antibodies in humans and in vitro detection assays, it may be preferable to use chimeric, humanized, or human antibodies. A chimeric antibody is a molecule in which different portions of the antibody are derived from different animal species, such as antibodies having a variable region derived from a murine monoclonal antibody and a human immunoglobulin constant region. Methods for producing chimeric antibodies are known in the art. See e.g., Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Gillies et al., (1989) J. Immunol. Methods 125:191-202; U.S. Patent Nos. 5,807,715; 4,816,567; and 4,816397, which are incorporated herein by reference in their entirety. Humanized antibodies are antibody molecules from non-human species antibody that binds the desired antigen having one or more complementarity determining regions (CDRs) from the non-human species and a framework regions from a human immunoglobulin molecule. Often, framework residues in the human framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter, preferably improve, antigen binding. These framework substitutions are identified by methods well known in the art, e.g., by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. (See, e.g., Queen et al., U.S. Patent No. 5,585,089; Riechmann et al., Nature 332:323 (1988), which are incorporated herein by reference in their entireties.) Antibodies can be humanized using a variety of techniques known in the art including, for example, CDR-grafting (EP 239,400; PCT publication WO 91/09967; U.S. Patent Nos. 5,225,539; 5,530,101; and 5,585,089), veneering or resurfacing (EP 592,106; EP 519,596; Padlan, Molecular Immunology 28(4/5):489-498 (1991); Studnicka et al., Protein Engineering 7(6):805-814 (1994); Roguska. et al., PNAS 91:969-973 (1994)), and chain shuffling (U.S. Patent No. 5,565,332).

[0171] Completely human antibodies are particularly desirable for therapeutic treatment of human patients. Human antibodies can be made by a variety of methods known in the art including phage display methods described above using antibody libraries derived from human immunoglobulin sequences. See also, U.S. Patent Nos. 4,444,887 and 4,716,111; and PCT publications WO 98/46645, WO 98/50433, WO 98/24893, WO 98/16654, WO 96/34096, WO 96/33735, and WO 91/10741; each of which is incorporated herein by reference in its entirety.

[0172] Human antibodies can also be produced using transgenic mice which are incapable of expressing functional endogenous immunoglobulins, but which can express human immunoglobulin genes. For example, the human heavy and light chain immunoglobulin gene complexes may be introduced randomly or by homologous recombination into mouse embryonic stem cells. Alternatively, the human variable region, constant region, and diversity region may be introduced into mouse embryonic stem cells in addition to the human heavy and light chain genes. The mouse heavy and light chain immunoglobulin genes may be rendered non-functional separately or simultaneously with the introduction of human immunoglobulin loci by homologous recombination. In particular, homozygous deletion of the JH region prevents endogenous antibody production. The modified embryonic stem cells are expanded and microinjected into blastocysts to produce chimeric mice. The chimeric mice are then bred to produce homozygous offspring which express human antibodies. The transgenic mice are immunized in the normal fashion with a selected antigen, e.g., all or a portion of a polypeptide of the invention. Monoclonal antibodies directed against the antigen can be obtained from the immunized, transgenic mice using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA, IgM and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar, Int. Rev. Immunol. 13:65-93 (1995). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, e.g., PCT publications WO 98/24893; WO 92/01047; WO 96/34096; WO 96/33735; European Patent No. 0 598 877; U.S. Patent Nos. 5,413,923; 5,625,126; 5,633,425; 5,569,825; 5,661,016; 5,545,806;

5,814,318; 5,885,793; 5,916,771; and 5,939,598, which are incorporated by reference herein in their entirety. In addition, companies such as Abgenix, Inc. (Freemont, CA) and Genpharm (San Jose, CA) can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

[0173] Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, e.g., a mouse antibody, is used to guide the selection of a completely human antibody recognizing the same epitope. (Jespers et al., Bio/technology 12:899-903 (1988)).

[0174] Further, antibodies to the polypeptides of the invention can, in turn, be utilized to generate anti-idiotype antibodies that "mimic" polypeptides of the invention using techniques well known to those skilled in the art. (See, e.g., Greenspan & Bona, FASEB J. 7(5):437-444; (1989) and Nissinoff, J. Immunol. 147(8):2429-2438 (1991)). For example, antibodies which bind to and competitively inhibit polypeptide multimerization and/or binding of a polypeptide of the invention to a ligand can be used to generate anti-idiotypes that "mimic" the polypeptide multimerization and/or binding domain and, as a consequence, bind to and neutralize polypeptide and/or its ligand. Such neutralizing anti-idiotypes or Fab fragments of such anti-idiotypes can be used in therapeutic regimens to neutralize polypeptide ligand. For example, such anti-idiotypic antibodies can be used to bind a polypeptide of the invention and/or to bind its ligands/receptors, and thereby block its biological activity.

Polynucleotides Encoding Antibodies

[0175] The invention further provides polynucleotides comprising a nucleotide sequence encoding an antibody of the invention and fragments thereof. The invention also encompasses polynucleotides that hybridize under stringent or alternatively, under lower stringency hybridization conditions, e.g., as defined supra, to polynucleotides that encode an antibody, preferably, that specifically binds to a polypeptide of the invention, preferably, an antibody that binds to a polypeptide having the amino acid sequence of SEQ ID NO:Y.

[0176] The polynucleotides may be obtained, and the nucleotide sequence of the polynucleotides determined, by any method known in the art. For example, if the

nucleotide sequence of the antibody is known, a polynucleotide encoding the antibody may be assembled from chemically synthesized oligonucleotides (e.g., as described in Kutmeier et al., BioTechniques 17:242 (1994)), which, briefly, involves the synthesis of overlapping oligonucleotides containing portions of the sequence encoding the antibody, annealing and ligating of those oligonucleotides, and then amplification of the ligated oligonucleotides by PCR.

[0177] Alternatively, a polynucleotide encoding an antibody may be generated from nucleic acid from a suitable source. If a clone containing a nucleic acid encoding a particular antibody is not available, but the sequence of the antibody molecule is known, a nucleic acid encoding the immunoglobulin may be chemically synthesized or obtained from a suitable source (e.g., an antibody cDNA library, or a cDNA library generated from, or nucleic acid, preferably poly A+ RNA, isolated from, any tissue or cells expressing the antibody, such as hybridoma cells selected to express an antibody of the invention) by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the sequence or by cloning using an oligonucleotide probe specific for the particular gene sequence to identify, e.g., a cDNA clone from a cDNA library that encodes the antibody. Amplified nucleic acids generated by PCR may then be cloned into replicable cloning vectors using any method well known in the art.

[0178] Once the nucleotide sequence and corresponding amino acid sequence of the antibody is determined, the nucleotide sequence of the antibody may be manipulated using methods well known in the art for the manipulation of nucleotide sequences, e.g., recombinant DNA techniques, site directed mutagenesis, PCR, etc. (see, for example, the techniques described in Sambrook et al., 1990, Molecular Cloning, A Laboratory Manual, 2d Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY and Ausubel et al., eds., 1998, Current Protocols in Molecular Biology, John Wiley & Sons, NY, which are both incorporated by reference herein in their entireties), to generate antibodies having a different amino acid sequence, for example to create amino acid substitutions, deletions, and/or insertions.

[0179] In a specific embodiment, the amino acid sequence of the heavy and/or light chain variable domains may be inspected to identify the sequences of the complementarity determining regions (CDRs) by methods that are well know in the art, e.g., by comparison to known amino acid sequences of other heavy and light chain

variable regions to determine the regions of sequence hypervariability. Using routine recombinant DNA techniques, one or more of the CDRs may be inserted within framework regions, e.g., into human framework regions to humanize a non-human antibody, as described supra. The framework regions may be naturally occurring or consensus framework regions, and preferably human framework regions (see, e.g., Chothia et al., J. Mol. Biol. 278: 457-479 (1998) for a listing of human framework regions). Preferably, the polynucleotide generated by the combination of the framework regions and CDRs encodes an antibody that specifically binds a polypeptide of the invention. Preferably, as discussed supra, one or more amino acid substitutions may be made within the framework regions, and, preferably, the amino acid substitutions improve binding of the antibody to its antigen. Additionally, such methods may be used to make amino acid substitutions or deletions of one or more variable region cysteine residues participating in an intrachain disulfide bond to generate antibody molecules lacking one or more intrachain disulfide bonds. Other alterations to the polynucleotide are encompassed by the present invention and within the skill of the art.

[0180] In addition, techniques developed for the production of "chimeric antibodies" (Morrison et al., Proc. Natl. Acad. Sci. 81:851-855 (1984); Neuberger et al., Nature 312:604-608 (1984); Takeda et al., Nature 314:452-454 (1985)) by splicing genes from a mouse antibody molecule of appropriate antigen specificity together with genes from a human antibody molecule of appropriate biological activity can be used. As described supra, a chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region, e.g., humanized antibodies.

[0181] Alternatively, techniques described for the production of single chain antibodies (U.S. Patent No. 4,946,778; Bird, Science 242:423- 42 (1988); Huston et al., Proc. Natl. Acad. Sci. USA 85:5879-5883 (1988); and Ward et al., Nature 334:544-54 (1989)) can be adapted to produce single chain antibodies. Single chain antibodies are formed by linking the heavy and light chain fragments of the Fv region via an amino acid bridge, resulting in a single chain polypeptide. Techniques for the assembly of functional Fv fragments in E. coli may also be used (Skerra et al., Science 242:1038- 1041 (1988)).

Methods of Producing Antibodies

[0182] The antibodies of the invention can be produced by any method known in the art for the synthesis of antibodies, in particular, by chemical synthesis or preferably, by recombinant expression techniques.

[0183] Recombinant expression of an antibody of the invention, or fragment, derivative or analog thereof, (e.g., a heavy or light chain of an antibody of the invention or a single chain antibody of the invention), requires construction of an expression vector containing a polynucleotide that encodes the antibody. Once a polynucleotide encoding an antibody molecule or a heavy or light chain of an antibody, or portion thereof (preferably containing the heavy or light chain variable domain), of the invention has been obtained, the vector for the production of the antibody molecule may be produced by recombinant DNA technology using techniques well known in the art. Thus, methods for preparing a protein by expressing a polynucleotide containing an antibody encoding nucleotide sequence are described herein. Methods which are well known to those skilled in the art can be used to construct expression vectors containing antibody coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. The invention, thus, provides replicable vectors comprising a nucleotide sequence encoding an antibody molecule of the invention, or a heavy or light chain thereof, or a heavy or light chain variable domain, operably linked to a promoter. Such vectors may include the nucleotide sequence encoding the constant region of the antibody molecule (see, e.g., PCT Publication WO 86/05807; PCT Publication WO 89/01036; and U.S. Patent No. 5,122,464) and the variable domain of the antibody may be cloned into such a vector for expression of the entire heavy or light chain.

[0184] The expression vector is transferred to a host cell by conventional techniques and the transfected cells are then cultured by conventional techniques to produce an antibody of the invention. Thus, the invention includes host cells containing a polynucleotide encoding an antibody of the invention, or a heavy or light chain thereof, or a single chain antibody of the invention, operably linked to a heterologous promoter. In preferred embodiments for the expression of double-chained antibodies, vectors encoding both the heavy and light chains may be co-expressed in the host cell for expression of the entire immunoglobulin molecule, as detailed below.

[0185] A variety of host-expression vector systems may be utilized to express the antibody molecules of the invention. Such host-expression systems represent vehicles by which the coding sequences of interest may be produced and subsequently purified, but also represent cells which may, when transformed or transfected with the appropriate nucleotide coding sequences, express an antibody molecule of the invention in situ. These include but are not limited to microorganisms such as bacteria (e.g., E. coli, B. subtilis) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing antibody coding sequences; yeast (e.g., Saccharomyces, Pichia) transformed with recombinant yeast expression vectors containing antibody coding sequences; insect cell systems infected with recombinant virus expression vectors (e.g., baculovirus) containing antibody coding sequences; plant cell systems infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid) containing antibody coding sequences; or mammalian cell systems (e.g., COS, CHO, BHK, 293, 3T3 cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (e.g., metallothionein promoter) or from mammalian viruses (e.g., the adenovirus late promoter; the vaccinia virus 7.5K promoter). Preferably, bacterial cells such as Escherichia coli, and more preferably, eukaryotic cells, especially for the expression of whole recombinant antibody molecule, are used for the expression of a recombinant antibody molecule. For example, mammalian cells such as Chinese hamster ovary cells (CHO), in conjunction with a vector such as the major intermediate early gene promoter element from human cytomegalovirus is an effective expression system for antibodies (Foecking et al., Gene 45:101 (1986); Cockett et al., Bio/Technology 8:2 (1990)).

[0186] In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the antibody molecule being expressed. For example, when a large quantity of such a protein is to be produced, for the generation of pharmaceutical compositions of an antibody molecule, vectors which direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited, to the E. coli expression vector pUR278 (Ruther et al., EMBO J. 2:1791 (1983)), in which the antibody coding sequence may be ligated individually into the vector in frame with the lac Z

coding region so that a fusion protein is produced; pIN vectors (Inouye & Inouye, Nucleic Acids Res. 13:3101-3109 (1985); Van Heeke & Schuster, J. Biol. Chem. 24:5503-5509 (1989)); and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption and binding to matrix glutathione-agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

[0187] In an insect system, Autographa californica nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells. The antibody coding sequence may be cloned individually into non-essential regions (for example the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example the polyhedrin promoter).

[0188] In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the antibody coding sequence of interest may be ligated to an adenovirus transcription/translation control complex, e.g., the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by in vitro or in vivo recombination. Insertion in a non- essential region of the viral genome (e.g., region E1 or E3) will result in a recombinant virus that is viable and capable of expressing the antibody molecule in infected hosts. (e.g., see Logan & Shenk, Proc. Natl. Acad. Sci. USA 81:355-359 (1984)). Specific initiation signals may also be required for efficient translation of inserted antibody coding sequences. These signals include the ATG initiation codon and adjacent sequences. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, etc. (see Bittner et al., Methods in Enzymol. 153:51-544 (1987)).

[0189] In addition, a host cell strain may be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (e.g., glycosylation) and processing (e.g.,

cleavage) of protein products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include but are not limited to CHO, VERY, BHK, Hela, COS, MDCK, 293, 3T3, WI38, and in particular, breast cancer cell lines such as, for example, BT483, Hs578T, HTB2, BT20 and T47D, and normal mammary gland cell line such as, for example, CRL7030 and Hs578Bst.

[0190] For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express the antibody molecule may be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (e.g., promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines which express the antibody molecule. Such engineered cell lines may be particularly useful in screening and evaluation of compounds that interact directly or indirectly with the antibody molecule.

[0191] A number of selection systems may be used, including but not limited to the herpes simplex virus thymidine kinase (Wigler et al., Cell 11:223 (1977)), hypoxanthine-guanine phosphoribosyltransferase (Szybalska & Szybalski, Proc. Natl. Acad. Sci. USA 48:202 (1992)), and adenine phosphoribosyltransferase (Lowy et al., Cell 22:817 (1980)) genes can be employed in tk-, hgprt- or aprt- cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: dhfr, which confers resistance to methotrexate (Wigler et al., Natl. Acad. Sci. USA 77:357 (1980); O'Hare et al., Proc. Natl. Acad. Sci. USA 78:1527 (1981)); gpt, which

confers resistance to mycophenolic acid (Mulligan & Berg, Proc. Natl. Acad. Sci. USA 78:2072 (1981)); neo, which confers resistance to the aminoglycoside G-418 Clinical Pharmacy 12:488-505; Wu and Wu, Biotherapy 3:87-95 (1991); Tolstoshev, Ann. Rev. Pharmacol. Toxicol. 32:573-596 (1993); Mulligan, Science 260:926-932 (1993); and Morgan and Anderson, Ann. Rev. Biochem. 62:191-217 (1993); May, 1993, TIB TECH 11(5):155-215); and hygro, which confers resistance to hygromycin (Santerre et al., Gene 30:147 (1984)). Methods commonly known in the art of recombinant DNA technology may be routinely applied to select the desired recombinant clone, and such methods are described, for example, in Ausubel et al. (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990); and in Chapters 12 and 13, Dracopoli et al. (eds), Current Protocols in Human Genetics, John Wiley & Sons, NY (1994); Colberre-Garapin et al., J. Mol. Biol. 150:1 (1981), which are incorporated by reference herein in their entireties.

[0192] The expression levels of an antibody molecule can be increased by vector amplification (for a review, see Bebbington and Hentschel, The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning, Vol.3. (Academic Press, New York, 1987)). When a marker in the vector system expressing antibody is amplifiable, increase in the level of inhibitor present in culture of host cell will increase the number of copies of the marker gene. Since the amplified region is associated with the antibody gene, production of the antibody will also increase (Crouse et al., Mol. Cell. Biol. 3:257 (1983)).

[0193] The host cell may be co-transfected with two expression vectors of the invention, the first vector encoding a heavy chain derived polypeptide and the second vector encoding a light chain derived polypeptide. The two vectors may contain identical selectable markers which enable equal expression of heavy and light chain polypeptides. Alternatively, a single vector may be used which encodes, and is capable of expressing, both heavy and light chain polypeptides. In such situations, the light chain should be placed before the heavy chain to avoid an excess of toxic free heavy chain (Proudfoot, Nature 322:52 (1986); Kohler, Proc. Natl. Acad. Sci. USA 77:2197 (1980)). The coding sequences for the heavy and light chains may comprise cDNA or genomic DNA.

[0194] Once an antibody molecule of the invention has been produced by an animal, chemically synthesized, or recombinantly expressed, it may be purified by any method known in the art for purification of an immunoglobulin molecule, for example, by chromatography (e.g., ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. In addition, the antibodies of the present invention or fragments thereof can be fused to heterologous polypeptide sequences described herein or otherwise known in the art, to facilitate purification.

[0195] The present invention encompasses antibodies recombinantly fused or chemically conjugated (including both covalently and non-covalently conjugations) to a polypeptide (or portion thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention to generate fusion proteins. The fusion does not necessarily need to be direct, but may occur through linker sequences. The antibodies may be specific for antigens other than polypeptides (or portion thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention. For example, antibodies may be used to target the polypeptides of the present invention to particular cell types, either in vitro or in vivo, by fusing or conjugating the polypeptides of the present invention to antibodies specific for particular cell surface receptors. Antibodies fused or conjugated to the polypeptides of the present invention may also be used in in vitro immunoassays and purification methods using methods known in the art. See e.g., Harbor et al., supra, and PCT publication WO 93/21232; EP 439,095; Naramura et al., Immunol. Lett. 39:91-99 (1994); U.S. Patent 5,474,981; Gillies et al., PNAS 89:1428-1432 (1992); Fell et al., J. Immunol. 146:2446-2452(1991), which are incorporated by reference in their entireties.

[0196] The present invention further includes compositions comprising the polypeptides of the present invention fused or conjugated to antibody domains other than the variable regions. For example, the polypeptides of the present invention may be fused or conjugated to an antibody Fc region, or portion thereof. The antibody portion fused to a polypeptide of the present invention may comprise the constant region, hinge region, CH1 domain, CH2 domain, and CH3 domain or any combination of whole domains or portions thereof. The polypeptides may also be fused or conjugated to the above antibody

portions to form multimers. For example, Fc portions fused to the polypeptides of the present invention can form dimers through disulfide bonding between the Fc portions. Higher multimeric forms can be made by fusing the polypeptides to portions of IgA and IgM. Methods for fusing or conjugating the polypeptides of the present invention to antibody portions are known in the art. See, e.g., U.S. Patent Nos. 5,336,603; 5,622,929; 5,359,046; 5,349,053; 5,447,851; 5,112,946; EP 307,434; EP 367,166; PCT publications WO 96/04388; WO 91/06570; Ashkenazi et al., Proc. Natl. Acad. Sci. USA 88:10535-10539 (1991); Zheng et al., J. Immunol. 154:5590-5600 (1995); and Vil et al., Proc. Natl. Acad. Sci. USA 89:11337- 11341(1992) (said references incorporated by reference in their entireties).

[0197] As discussed, supra, the polypeptides corresponding to a polypeptide, polypeptide fragment, or a variant of SEQ ID NO:Y may be fused or conjugated to the above antibody portions to increase the in vivo half life of the polypeptides or for use in immunoassays using methods known in the art. Further, the polypeptides corresponding to SEQ ID NO:Y may be fused or conjugated to the above antibody portions to facilitate purification. One reported example describes chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. (EP 394,827; Traunecker et al., Nature 331:84-86 (1988). The polypeptides of the present invention fused or conjugated to an antibody having disulfide- linked dimeric structures (due to the IgG) may also be more efficient in binding and neutralizing other molecules, than the monomeric secreted protein or protein fragment alone. (Fountoulakis et al., J. Biochem. 270:3958-3964 (1995)). In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. (EP A 232,262). Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See, Bennett et al., J. Molecular Recognition 8:52-58 (1995); Johanson et al., J. Biol. Chem. 270:9459-9471 (1995).

[0198] Moreover, the antibodies or fragments thereof of the present invention can be fused to marker sequences, such as a peptide to facilitate purification. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the "HA" tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., Cell 37:767 (1984)) and the "flag" tag.

[0199] The present invention further encompasses antibodies or fragments thereof conjugated to a diagnostic or therapeutic agent. The antibodies can be used diagnostically to, for example, monitor the development or progression of a tumor as part of a clinical testing procedure to, e.g., determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, radioactive materials, positron emitting metals using various positron emission tomographies, and nonradioactive paramagnetic metal ions. The detectable substance may be coupled or conjugated either directly to the antibody (or fragment thereof) or indirectly, through an intermediate (such as, for example, a linker known in the art) using techniques known in the art. See, for example, U.S. Patent No. 4,741,900 for metal ions which can be conjugated to antibodies for use as diagnostics according to the present invention. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin; and examples of suitable radioactive material include 125I, 131I, 111In or 99Tc.

[0200] Further, an antibody or fragment thereof may be conjugated to a therapeutic moiety such as a cytotoxin, e.g., a cytostatic or cytocidal agent, a therapeutic

agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, 213Bi. A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclothosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis- dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine).

[0201] The conjugates of the invention can be used for modifying a given biological response, the therapeutic agent or drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor, a-interferon, ß-interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, e.g., TNF-alpha, TNF-beta, AIM I (See, International Publication No. WO 97/33899), AIM II (See, International Publication No. WO 97/34911), Fas Ligand (Takahashi *et al., Int. Immunol.,* 6:1567-1574 (1994)), VEGI (See, International Publication No. WO 99/23105), a thrombotic agent or an anti- angiogenic agent, e.g., angiostatin or endostatin; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

[0202] Antibodies may also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports

include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

[0203] Techniques for conjugating such therapeutic moiety to antibodies are well known, see, e.g., Arnon et al., "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in Monoclonal Antibodies And Cancer Therapy, Reisfeld et al. (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom et al., "Antibodies For Drug Delivery", in Controlled Drug Delivery (2nd Ed.), Robinson et al. (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in Monoclonal Antibodies '84: Biological And Clinical Applications, Pinchera et al. (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in Monoclonal Antibodies For Cancer Detection And Therapy, Baldwin et al. (eds.), pp. 303-16 (Academic Press 1985), and Thorpe et al., "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", Immunol. Rev. 62:119-58 (1982).

[0204] Alternatively, an antibody can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980, which is incorporated herein by reference in its entirety.

[0205] An antibody, with or without a therapeutic moiety conjugated to it, administered alone or in combination with cytotoxic factor(s) and/or cytokine(s) can be used as a therapeutic.

Immunophenotyping

[0206] The antibodies of the invention may be utilized for immunophenotyping of cell lines and biological samples. The translation product of the gene of the present invention may be useful as a cell specific marker, or more specifically as a cellular marker that is differentially expressed at various stages of differentiation and/or maturation of particular cell types. Monoclonal antibodies directed against a specific epitope, or combination of epitopes, will allow for the screening of cellular populations expressing the marker. Various techniques can be utilized using monoclonal antibodies to screen for cellular populations expressing the marker(s), and include magnetic separation using antibody-coated magnetic beads, "panning" with antibody attached to a solid matrix (i.e.,

plate), and flow cytometry (See, e.g., U.S. Patent 5,985,660; and Morrison *et al., Cell, 96*:737-49 (1999)).

[0207] These techniques allow for the screening of particular populations of cells, such as might be found with hematological malignancies (i.e. minimal residual disease (MRD) in acute leukemic patients) and "non-self" cells in transplantations to prevent Graft-versus-Host Disease (GVHD). Alternatively, these techniques allow for the screening of hematopoietic stem and progenitor cells capable of undergoing proliferation and/or differentiation, as might be found in human umbilical cord blood.

Assays For Antibody Binding

[0208] The antibodies of the invention may be assayed for immunospecific binding by any method known in the art. The immunoassays which can be used include but are not limited to competitive and non-competitive assay systems using techniques such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, protein A immunoassays, to name but a few. Such assays are routine and well known in the art (see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, which is incorporated by reference herein in its entirety). Exemplary immunoassays are described briefly below (but are not intended by way of limitation).

[0209] Immunoprecipitation protocols generally comprise lysing a population of cells in a lysis buffer such as RIPA buffer (1% NP-40 or Triton X- 100, 1% sodium deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1% Trasylol) supplemented with protein phosphatase and/or protease inhibitors (e.g., EDTA, PMSF, aprotinin, sodium vanadate), adding the antibody of interest to the cell lysate, incubating for a period of time (e.g., 1-4 hours) at 4° C, adding protein A and/or protein G sepharose beads to the cell lysate, incubating for about an hour or more at 4° C, washing the beads in lysis buffer and resuspending the beads in SDS/sample buffer. The ability of the antibody of interest to immunoprecipitate a particular antigen can be assessed by, e.g., western blot analysis. One of skill in the art would be knowledgeable as to the parameters

that can be modified to increase the binding of the antibody to an antigen and decrease the background (e.g., pre-clearing the cell lysate with sepharose beads). For further discussion regarding immunoprecipitation protocols see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.16.1.

[0210] Western blot analysis generally comprises preparing protein samples, electrophoresis of the protein samples in a polyacrylamide gel (e.g., 8%- 20% SDS-PAGE depending on the molecular weight of the antigen), transferring the protein sample from the polyacrylamide gel to a membrane such as nitrocellulose, PVDF or nylon, blocking the membrane in blocking solution (e.g., PBS with 3% BSA or non-fat milk), washing the membrane in washing buffer (e.g., PBS-Tween 20), blocking the membrane with primary antibody (the antibody of interest) diluted in blocking buffer, washing the membrane in washing buffer, blocking the membrane with a secondary antibody (which recognizes the primary antibody, e.g., an anti-human antibody) conjugated to an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) or radioactive molecule (e.g., 32P or 125I) diluted in blocking buffer, washing the membrane in wash buffer, and detecting the presence of the antigen. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected and to reduce the background noise. For further discussion regarding western blot protocols see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.8.1.

[0211] ELISAs comprise preparing antigen, coating the well of a 96 well microtiter plate with the antigen, adding the antibody of interest conjugated to a detectable compound such as an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) to the well and incubating for a period of time, and detecting the presence of the antigen. In ELISAs the antibody of interest does not have to be conjugated to a detectable compound; instead, a second antibody (which recognizes the antibody of interest) conjugated to a detectable compound may be added to the well. Further, instead of coating the well with the antigen, the antibody may be coated to the well. In this case, a second antibody conjugated to a detectable compound may be added following the addition of the antigen of interest to the coated well. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal

detected as well as other variations of ELISAs known in the art. For further discussion regarding ELISAs see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 11.2.1.

[0212] The binding affinity of an antibody to an antigen and the off-rate of an antibody-antigen interaction can be determined by competitive binding assays. One example of a competitive binding assay is a radioimmunoassay comprising the incubation of labeled antigen (e.g., 3H or 125I) with the antibody of interest in the presence of increasing amounts of unlabeled antigen, and the detection of the antibody bound to the labeled antigen. The affinity of the antibody of interest for a particular antigen and the binding off-rates can be determined from the data by scatchard plot analysis. Competition with a second antibody can also be determined using radioimmunoassays. In this case, the antigen is incubated with antibody of interest conjugated to a labeled compound (e.g., 3H or 125I) in the presence of increasing amounts of an unlabeled second antibody.

Therapeutic Uses

[0213] The present invention is further directed to antibody-based therapies which involve administering antibodies of the invention to an animal, preferably a mammal, and most preferably a human, patient for treating one or more of the disclosed diseases, disorders, or conditions. Therapeutic compounds of the invention include, but are not limited to, antibodies of the invention (including fragments, analogs and derivatives thereof as described herein) and nucleic acids encoding antibodies of the invention (including fragments, analogs and derivatives thereof and anti-idiotypic antibodies as described herein). The antibodies of the invention can be used to treat, inhibit or prevent diseases, disorders or conditions associated with aberrant expression and/or activity of a polypeptide of the invention, including, but not limited to, any one or more of the diseases, disorders, or conditions described herein. The treatment and/or prevention of diseases, disorders, or conditions associated with aberrant expression and/or activity of a polypeptide of the invention includes, but is not limited to, alleviating symptoms associated with those diseases, disorders or conditions. Antibodies of the invention may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

[0214] A summary of the ways in which the antibodies of the present invention may be used therapeutically includes binding polynucleotides or polypeptides of the present invention locally or systemically in the body or by direct cytotoxicity of the antibody, e.g. as mediated by complement (CDC) or by effector cells (ADCC). Some of these approaches are described in more detail below. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of the present invention for diagnostic, monitoring or therapeutic purposes without undue experimentation.

[0215] The antibodies of this invention may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors (such as, e.g., IL-2, IL-3 and IL-7), for example, which serve to increase the number or activity of effector cells which interact with the antibodies.

[0216] The antibodies of the invention may be administered alone or in combination with other types of treatments (e.g., radiation therapy, chemotherapy, hormonal therapy, immunotherapy and anti-tumor agents). Generally, administration of products of a species origin or species reactivity (in the case of antibodies) that is the same species as that of the patient is preferred. Thus, in a preferred embodiment, human antibodies, fragments derivatives, analogs, or nucleic acids, are administered to a human patient for therapy or prophylaxis.

[0217] It is preferred to use high affinity and/or potent in vivo inhibiting and/or neutralizing antibodies against polypeptides or polynucleotides of the present invention, fragments or regions thereof, for both immunoassays directed to and therapy of disorders related to polynucleotides or polypeptides, including fragments thereof, of the present invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides of the invention, including fragments thereof. Preferred binding affinities include those with a dissociation constant or Kd less than 5×10^{-2} M, 10^{-2} M, 5×10^{-3} M, 10^{-3} M, 5×10^{-4} M, 10^{-4} M, 5×10^{-5} M, 10^{-5} M, 5×10^{-6} M, 10^{-6} M, 5×10^{-7} M, 10^{-7} M, 5×10^{-8} M, 10^{-8} M, 5×10^{-9} M, 10^{-9} M, 5×10^{-10} M, 10^{-10} M, 5×10^{-11} M, 10^{-11} M, 5×10^{-12} M, 10^{-12} M, 5×10^{-13} M, 10^{-13} M, 5×10^{-14} M, 10^{-14} M, 5×10^{-15} M, and 10^{-15} M.

Gene Therapy

[0218] In a specific embodiment, nucleic acids comprising sequences encoding antibodies or functional derivatives thereof, are administered to treat, inhibit or prevent a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention, by way of gene therapy. Gene therapy refers to therapy performed by the administration to a subject of an expressed or expressible nucleic acid. In this embodiment of the invention, the nucleic acids produce their encoded protein that mediates a therapeutic effect.

[0219] Any of the methods for gene therapy available in the art can be used according to the present invention. Exemplary methods are described below.

[0220] For general reviews of the methods of gene therapy, see Goldspiel et al., Clinical Pharmacy 12:488-505 (1993); Wu and Wu, Biotherapy 3:87-95 (1991); Tolstoshev, Ann. Rev. Pharmacol. Toxicol. 32:573-596 (1993); Mulligan, Science 260:926-932 (1993); and Morgan and Anderson, Ann. Rev. Biochem. 62:191-217 (1993); May, TIBTECH 11(5):155-215 (1993). Methods commonly known in the art of recombinant DNA technology which can be used are described in Ausubel et al. (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); and Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990).

[0221] In a preferred aspect, the compound comprises nucleic acid sequences encoding an antibody, said nucleic acid sequences being part of expression vectors that express the antibody or fragments or chimeric proteins or heavy or light chains thereof in a suitable host. In particular, such nucleic acid sequences have promoters operably linked to the antibody coding region, said promoter being inducible or constitutive, and, optionally, tissue-specific. In another particular embodiment, nucleic acid molecules are used in which the antibody coding sequences and any other desired sequences are flanked by regions that promote homologous recombination at a desired site in the genome, thus providing for intrachromosomal expression of the antibody encoding nucleic acids (Koller and Smithies, Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); Zijlstra et al., Nature 342:435-438 (1989). In specific embodiments, the expressed antibody molecule is a single chain antibody; alternatively, the nucleic acid sequences include sequences encoding both the heavy and light chains, or fragments thereof, of the antibody.

[0222] Delivery of the nucleic acids into a patient may be either direct, in which case the patient is directly exposed to the nucleic acid or nucleic acid- carrying vectors, or indirect, in which case, cells are first transformed with the nucleic acids in vitro, then transplanted into the patient. These two approaches are known, respectively, as in vivo or ex vivo gene therapy.

[0223] In a specific embodiment, the nucleic acid sequences are directly administered in vivo, where it is expressed to produce the encoded product. This can be accomplished by any of numerous methods known in the art, e.g., by constructing them as part of an appropriate nucleic acid expression vector and administering it so that they become intracellular, e.g., by infection using defective or attenuated retrovirals or other viral vectors (see U.S. Patent No. 4,980,286), or by direct injection of naked DNA, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, encapsulation in liposomes, microparticles, or microcapsules, or by administering them in linkage to a peptide which is known to enter the nucleus, by administering it in linkage to a ligand subject to receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)) (which can be used to target cell types specifically expressing the receptors), etc. In another embodiment, nucleic acid-ligand complexes can be formed in which the ligand comprises a fusogenic viral peptide to disrupt endosomes, allowing the nucleic acid to avoid lysosomal degradation. In yet another embodiment, the nucleic acid can be targeted in vivo for cell specific uptake and expression, by targeting a specific receptor (see, e.g., PCT Publications WO 92/06180; WO 92/22635; WO92/20316; WO93/14188, WO 93/20221). Alternatively, the nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination (Koller and Smithies, Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); Zijlstra et al., Nature 342:435-438 (1989)).

[0224] In a specific embodiment, viral vectors that contains nucleic acid sequences encoding an antibody of the invention are used. For example, a retroviral vector can be used (see Miller et al., Meth. Enzymol. 217:581-599 (1993)). These retroviral vectors contain the components necessary for the correct packaging of the viral genome and integration into the host cell DNA. The nucleic acid sequences encoding the antibody to be used in gene therapy are cloned into one or more vectors, which facilitates delivery of

the gene into a patient. More detail about retroviral vectors can be found in Boesen et al., Biotherapy 6:291-302 (1994), which describes the use of a retroviral vector to deliver the mdr1 gene to hematopoietic stem cells in order to make the stem cells more resistant to chemotherapy. Other references illustrating the use of retroviral vectors in gene therapy are: Clowes et al., J. Clin. Invest. 93:644-651 (1994); Kiem et al., Blood 83:1467-1473 (1994); Salmons and Gunzberg, Human Gene Therapy 4:129-141 (1993); and Grossman and Wilson, Curr. Opin. in Genetics and Devel. 3:110-114 (1993).

[0225] Adenoviruses are other viral vectors that can be used in gene therapy. Adenoviruses are especially attractive vehicles for delivering genes to respiratory epithelia. Adenoviruses naturally infect respiratory epithelia where they cause a mild disease. Other targets for adenovirus-based delivery systems are liver, the central nervous system, endothelial cells, and muscle. Adenoviruses have the advantage of being capable of infecting non-dividing cells. Kozarsky and Wilson, Current Opinion in Genetics and Development 3:499-503 (1993) present a review of adenovirus-based gene therapy. Bout et al., Human Gene Therapy 5:3-10 (1994) demonstrated the use of adenovirus vectors to transfer genes to the respiratory epithelia of rhesus monkeys. Other instances of the use of adenoviruses in gene therapy can be found in Rosenfeld et al., Science 252:431-434 (1991); Rosenfeld et al., Cell 68:143- 155 (1992); Mastrangeli et al., J. Clin. Invest. 91:225-234 (1993); PCT Publication WO94/12649; and Wang, et al., Gene Therapy 2:775-783 (1995). In a preferred embodiment, adenovirus vectors are used.

[0226] Adeno-associated virus (AAV) has also been proposed for use in gene therapy (Walsh et al., Proc. Soc. Exp. Biol. Med. 204:289-300 (1993); U.S. Patent No. 5,436,146).

[0227] Another approach to gene therapy involves transferring a gene to cells in tissue culture by such methods as electroporation, lipofection, calcium phosphate mediated transfection, or viral infection. Usually, the method of transfer includes the transfer of a selectable marker to the cells. The cells are then placed under selection to isolate those cells that have taken up and are expressing the transferred gene. Those cells are then delivered to a patient.

[0228] In this embodiment, the nucleic acid is introduced into a cell prior to administration in vivo of the resulting recombinant cell. Such introduction can be carried out by any method known in the art, including but not limited to transfection,

electroporation, microinjection, infection with a viral or bacteriophage vector containing the nucleic acid sequences, cell fusion, chromosome-mediated gene transfer, microcell-mediated gene transfer, spheroplast fusion, etc. Numerous techniques are known in the art for the introduction of foreign genes into cells (see, e.g., Loeffler and Behr, Meth. Enzymol. 217:599-618 (1993); Cohen et al., Meth. Enzymol. 217:618-644 (1993); Cline, Pharmac. Ther. 29:69-92m (1985) and may be used in accordance with the present invention, provided that the necessary developmental and physiological functions of the recipient cells are not disrupted. The technique should provide for the stable transfer of the nucleic acid to the cell, so that the nucleic acid is expressible by the cell and preferably heritable and expressible by its cell progeny.

[0229] The resulting recombinant cells can be delivered to a patient by various methods known in the art. Recombinant blood cells (e.g., hematopoietic stem or progenitor cells) are preferably administered intravenously. The amount of cells envisioned for use depends on the desired effect, patient state, etc., and can be determined by one skilled in the art.

[0230] Cells into which a nucleic acid can be introduced for purposes of gene therapy encompass any desired, available cell type, and include but are not limited to epithelial cells, endothelial cells, keratinocytes, fibroblasts, muscle cells, hepatocytes; blood cells such as Tlymphocytes, Blymphocytes, monocytes, macrophages, neutrophils, eosinophils, megakaryocytes, granulocytes; various stem or progenitor cells, in particular hematopoietic stem or progenitor cells, e.g., as obtained from bone marrow, umbilical cord blood, peripheral blood, fetal liver, etc.

[0231] In a preferred embodiment, the cell used for gene therapy is autologous to the patient.

[0232] In an embodiment in which recombinant cells are used in gene therapy, nucleic acid sequences encoding an antibody are introduced into the cells such that they are expressible by the cells or their progeny, and the recombinant cells are then administered in vivo for therapeutic effect. In a specific embodiment, stem or progenitor cells are used. Any stem and/or progenitor cells which can be isolated and maintained in vitro can potentially be used in accordance with this embodiment of the present invention (see e.g. PCT Publication WO 94/08598; Stemple and Anderson, Cell 71:973-985 (1992);

Rheinwald, Meth. Cell Bio. 21A:229 (1980); and Pittelkow and Scott, Mayo Clinic Proc. 61:771 (1986)).

[0233] In a specific embodiment, the nucleic acid to be introduced for purposes of gene therapy comprises an inducible promoter operably linked to the coding region, such that expression of the nucleic acid is controllable by controlling the presence or absence of the appropriate inducer of transcription. Demonstration of Therapeutic or Prophylactic Activity

[0234] The compounds or pharmaceutical compositions of the invention are preferably tested in vitro, and then in vivo for the desired therapeutic or prophylactic activity, prior to use in humans. For example, in vitro assays to demonstrate the therapeutic or prophylactic utility of a compound or pharmaceutical composition include, the effect of a compound on a cell line or a patient tissue sample. The effect of the compound or composition on the cell line and/or tissue sample can be determined utilizing techniques known to those of skill in the art including, but not limited to, rosette formation assays and cell lysis assays. In accordance with the invention, in vitro assays which can be used to determine whether administration of a specific compound is indicated, include in vitro cell culture assays in which a patient tissue sample is grown in culture, and exposed to or otherwise administered a compound, and the effect of such compound upon the tissue sample is observed.

Therapeutic/Prophylactic Administration and Composition

[0235] The invention provides methods of treatment, inhibition and prophylaxis by administration to a subject of an effective amount of a compound or pharmaceutical composition of the invention, preferably a polypeptide or antibody of the invention. In a preferred aspect, the compound is substantially purified (e.g., substantially free from substances that limit its effect or produce undesired side-effects). The subject is preferably an animal, including but not limited to animals such as cows, pigs, horses, chickens, cats, dogs, etc., and is preferably a mammal, and most preferably human.

[0236] Formulations and methods of administration that can be employed when the compound comprises a nucleic acid or an immunoglobulin are described above; additional appropriate formulations and routes of administration can be selected from among those described herein below.

[0237] Various delivery systems are known and can be used to administer a compound of the invention, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the compound, receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of introduction include but are not limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The compounds or compositions may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, it may be desirable to introduce the pharmaceutical compounds or compositions of the invention into the central nervous system by any suitable route, including intraventricular and intrathecal injection; intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir. Pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

[0238] In a specific embodiment, it may be desirable to administer the pharmaceutical compounds or compositions of the invention locally to the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion during surgery, topical application, e.g., in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. Preferably, when administering a protein, including an antibody, of the invention, care must be taken to use materials to which the protein does not absorb.

[0239] In another embodiment, the compound or composition can be delivered in a vesicle, in particular a liposome (see Langer, Science 249:1527-1533 (1990); Treat et al., in Liposomes in the Therapy of Infectious Disease and Cancer, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353- 365 (1989); Lopez-Berestein, ibid., pp. 317-327; see generally ibid.)

[0240] In yet another embodiment, the compound or composition can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, supra; Sefton, CRC Crit. Ref. Biomed. Eng. 14:201 (1987); Buchwald et al., Surgery 88:507 (1980); Saudek et al., N. Engl. J. Med. 321:574 (1989)). In another embodiment, polymeric materials can be used (see Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); Controlled Drug Bioavailability, Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, J., Macromol. Sci. Rev. Macromol. Chem. 23:61 (1983); see also Levy et al., Science 228:190 (1985); During et al., Ann. Neurol. 25:351 (1989); Howard et al., J.Neurosurg. 71:105 (1989)). In yet another embodiment, a controlled release system can be placed in proximity of the therapeutic target, i.e., the brain, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in Medical Applications of Controlled Release, supra, vol. 2, pp. 115-138 (1984)).

[0241] Other controlled release systems are discussed in the review by Langer (Science 249:1527-1533 (1990)).

[0242] In a specific embodiment where the compound of the invention is a nucleic acid encoding a protein, the nucleic acid can be administered in vivo to promote expression of its encoded protein, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, e.g., by use of a retroviral vector (see U.S. Patent No. 4,980,286), or by direct injection, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox- like peptide which is known to enter the nucleus (see e.g., Joliot et al., Proc. Natl. Acad. Sci. USA 88:1864-1868 (1991)), etc. Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

[0243] The present invention also provides pharmaceutical compositions. Such compositions comprise a therapeutically effective amount of a compound, and a pharmaceutically acceptable carrier. In a specific embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier"

refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. Such compositions will contain a therapeutically effective amount of the compound, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

[0244] In a preferred embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water

for injection or saline can be provided so that the ingredients may be mixed prior to administration.

[0245] The compounds of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

[0246] The amount of the compound of the invention which will be effective in the treatment, inhibition and prevention of a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention can be determined by standard clinical techniques. In addition, in vitro assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems.

[0247] For antibodies, the dosage administered to a patient is typically 0.1 mg/kg to 100 mg/kg of the patient's body weight. Preferably, the dosage administered to a patient is between 0.1 mg/kg and 20 mg/kg of the patient's body weight, more preferably 1 mg/kg to 10 mg/kg of the patient's body weight. Generally, human antibodies have a longer half-life within the human body than antibodies from other species due to the immune response to the foreign polypeptides. Thus, lower dosages of human antibodies and less frequent administration is often possible. Further, the dosage and frequency of administration of antibodies of the invention may be reduced by enhancing uptake and tissue penetration (e.g., into the brain) of the antibodies by modifications such as, for example, lipidation.

[0248] The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

Diagnosis and Imaging

[0249] Labeled antibodies, and derivatives and analogs thereof, which specifically bind to a polypeptide of interest can be used for diagnostic purposes to detect, diagnose, or monitor diseases, disorders, and/or conditions associated with the aberrant expression and/or activity of a polypeptide of the invention. The invention provides for the detection of aberrant expression of a polypeptide of interest, comprising (a) assaying the expression of the polypeptide of interest in cells or body fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of aberrant expression.

[0250] The invention provides a diagnostic assay for diagnosing a disorder, comprising (a) assaying the expression of the polypeptide of interest in cells or body fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of a particular disorder. With respect to cancer, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

[0251] Antibodies of the invention can be used to assay protein levels in a biological sample using classical immunohistological methods known to those of skill in the art (e.g., see Jalkanen, et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, et al., J. Cell . Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine (125I, 121I), carbon (14C), sulfur (35S), tritium (3H), indium (112In), and

technetium (99Tc); luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[0252] One aspect of the invention is the detection and diagnosis of a disease or disorder associated with aberrant expression of a polypeptide of interest in an animal, preferably a mammal and most preferably a human. In one embodiment, diagnosis comprises: a) administering (for example, parenterally, subcutaneously, or intraperitoneally) to a subject an effective amount of a labeled molecule which specifically binds to the polypeptide of interest; b) waiting for a time interval following the administering for permitting the labeled molecule to preferentially concentrate at sites in the subject where the polypeptide is expressed (and for unbound labeled molecule to be cleared to background level); c) determining background level; and d) detecting the labeled molecule in the subject, such that detection of labeled molecule above the background level indicates that the subject has a particular disease or disorder associated with aberrant expression of the polypeptide of interest. Background level can be determined by various methods including, comparing the amount of labeled molecule detected to a standard value previously determined for a particular system.

[0253] It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of 99mTc. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the specific protein. In vivo tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982).

[0254] Depending on several variables, including the type of label used and the mode of administration, the time interval following the administration for permitting the labeled molecule to preferentially concentrate at sites in the subject and for unbound labeled molecule to be cleared to background level is 6 to 48 hours or 6 to 24 hours or 6 to 12 hours. In another embodiment the time interval following administration is 5 to 20 days or 5 to 10 days.

[0255] In an embodiment, monitoring of the disease or disorder is carried out by repeating the method for diagnosing the disease or disease, for example, one month after initial diagnosis, six months after initial diagnosis, one year after initial diagnosis, etc.

[0256] Presence of the labeled molecule can be detected in the patient using methods known in the art for in vivo scanning. These methods depend upon the type of label used. Skilled artisans will be able to determine the appropriate method for detecting a particular label. Methods and devices that may be used in the diagnostic methods of the invention include, but are not limited to, computed tomography (CT), whole body scan such as position emission tomography (PET), magnetic resonance imaging (MRI), and sonography.

[0257] In a specific embodiment, the molecule is labeled with a radioisotope and is detected in the patient using a radiation responsive surgical instrument (Thurston et al., U.S. Patent No. 5,441,050). In another embodiment, the molecule is labeled with a fluorescent compound and is detected in the patient using a fluorescence responsive scanning instrument. In another embodiment, the molecule is labeled with a positron emitting metal and is detected in the patent using positron emission-tomography. In yet another embodiment, the molecule is labeled with a paramagnetic label and is detected in a patient using magnetic resonance imaging (MRI).

Kits

[0258] The present invention provides kits that can be used in the above methods. In one embodiment, a kit comprises an antibody of the invention, preferably a purified antibody, in one or more containers. In a specific embodiment, the kits of the present invention contain a substantially isolated polypeptide comprising an epitope which is specifically immunoreactive with an antibody included in the kit. Preferably, the kits of the present invention further comprise a control antibody which does not react with the polypeptide of interest. In another specific embodiment, the kits of the present invention contain a means for detecting the binding of an antibody to a polypeptide of interest (e.g., the antibody may be conjugated to a detectable substrate such as a fluorescent compound, an enzymatic substrate, a radioactive compound or a luminescent compound, or a second antibody which recognizes the first antibody may be conjugated to a detectable substrate).

[0259] In another specific embodiment of the present invention, the kit is a diagnostic kit for use in screening serum containing antibodies specific against proliferative and/or cancerous polynucleotides and polypeptides. Such a kit may include a control antibody that does not react with the polypeptide of interest. Such a kit may include a substantially isolated polypeptide antigen comprising an epitope which is specifically immunoreactive with at least one anti-polypeptide antigen antibody. Further, such a kit includes means for detecting the binding of said antibody to the antigen (e.g., the antibody may be conjugated to a fluorescent compound such as fluorescein or rhodamine which can be detected by flow cytometry). In specific embodiments, the kit may include a recombinantly produced or chemically synthesized polypeptide antigen. The polypeptide antigen of the kit may also be attached to a solid support.

[0260] In a more specific embodiment the detecting means of the above-described kit includes a solid support to which said polypeptide antigen is attached. Such a kit may also include a non-attached reporter-labeled anti-human antibody. In this embodiment, binding of the antibody to the polypeptide antigen can be detected by binding of the said reporter-labeled antibody.

[0261] In an additional embodiment, the invention includes a diagnostic kit for use in screening serum containing antigens of the polypeptide of the invention. The diagnostic kit includes a substantially isolated antibody specifically immunoreactive with polypeptide or polynucleotide antigens, and means for detecting the binding of the polynucleotide or polypeptide antigen to the antibody. In one embodiment, the antibody is attached to a solid support. In a specific embodiment, the antibody may be a monoclonal antibody. The detecting means of the kit may include a second, labeled monoclonal antibody. Alternatively, or in addition, the detecting means may include a labeled, competing antigen.

[0262] In one diagnostic configuration, test serum is reacted with a solid phase reagent having a surface-bound antigen obtained by the methods of the present invention. After binding with specific antigen antibody to the reagent and removing unbound serum components by washing, the reagent is reacted with reporter-labeled anti-human antibody to bind reporter to the reagent in proportion to the amount of bound anti-antigen antibody on the solid support. The reagent is again washed to remove unbound labeled antibody, and the amount of reporter associated with the reagent is determined. Typically, the

reporter is an enzyme which is detected by incubating the solid phase in the presence of a suitable fluorometric, luminescent or colorimetric substrate (Sigma, St. Louis, MO).

[0263] The solid surface reagent in the above assay is prepared by known techniques for attaching protein material to solid support material, such as polymeric beads, dip sticks, 96-well plate or filter material. These attachment methods generally include non-specific adsorption of the protein to the support or covalent attachment of the protein, typically through a free amine group, to a chemically reactive group on the solid support, such as an activated carboxyl, hydroxyl, or aldehyde group. Alternatively, streptavidin coated plates can be used in conjunction with biotinylated antigen(s).

[0264] Thus, the invention provides an assay system or kit for carrying out this diagnostic method. The kit generally includes a support with surface- bound recombinant antigens, and a reporter-labeled anti-human antibody for detecting surface-bound anti-antigen antibody.

Uses of the Polynucleotides

[0265] Each of the polynucleotides identified herein can be used in numerous ways as reagents. The following description should be considered exemplary and utilizes known techniques.

[0266] The prostate cancer antigen polynucleotides of the present invention are useful for chromosome identification. There exists an ongoing need to identify new chromosome markers, since few chromosome marking reagents, based on actual sequence data (repeat polymorphisms), are presently available. Each sequence is specifically targeted to and can hybridize with a particular location on an individual human chromosome, thus each polynucleotide of the present invention can routinely be used as a chromosome marker using techniques known in the art.

[0267] Briefly, sequences can be mapped to chromosomes by preparing PCR primers (preferably at least 15 bp (e.g., 15-25 bp) from the sequences shown in SEQ ID NO:X, or the complement thereto. Primers can optionally be selected using computer analysis so that primers do not span more than one predicted exon in the genomic DNA. These primers are then used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to SEQ ID NO:X will yield an amplified fragment.

[0268] Similarly, somatic hybrids provide a rapid method of PCR mapping the polynucleotides to particular chromosomes. Three or more clones can be assigned per day using a single thermal cycler. Moreover, sublocalization of the polynucleotides can be achieved with panels of specific chromosome fragments. Other gene mapping strategies that can be used include in situ hybridization, prescreening with labeled flow-sorted chromosomes, preselection by hybridization to construct chromosome specific-cDNA libraries, and computer mapping techniques (See, e.g., Shuler, Trends Biotechnol 16:456-459 (1998) which is hereby incorporated by reference in its entirety).

[0269] Precise chromosomal location of the polynucleotides can also be achieved using fluorescence in situ hybridization (FISH) of a metaphase chromosomal spread. This technique uses polynucleotides as short as 500 or 600 bases; however, polynucleotides 2,000-4,000 bp are preferred. For a review of this technique, see Verma et al., "Human Chromosomes: a Manual of Basic Techniques," Pergamon Press, New York (1988).

[0270] For chromosome mapping, the polynucleotides can be used individually (to mark a single chromosome or a single site on that chromosome) or in panels (for marking multiple sites and/or multiple chromosomes).

[0271] Thus, the present invention also provides a method for chromosomal localization which involves (a) preparing PCR primers from the polynucleotide sequences in Table 3 and SEQ ID NO:X and (b) screening somatic cell hybrids containing individual chromosomes.

[0272] The polynucleotides of the present invention would likewise be useful for radiation hybrid mapping, HAPPY mapping, and long range restriction mapping. For a review of these techniques and others known in the art, see, e.g. Dear, "Genome Mapping: A Practical Approach," IRL Press at Oxford University Press, London (1997); Aydin, J. Mol. Med. 77:691-694 (1999); Hacia et al., Mol. Psychiatry 3:483-492 (1998); Herrick et al., Chromosome Res. 7:409-423 (1999); Hamilton et al., Methods Cell Biol. 62:265-280 (2000); and/or Ott, J. Hered. 90:68-70 (1999) each of which is hereby incorporated by reference in its entirety.

[0273] Once a polynucleotide has been mapped to a precise chromosomal location, the physical position of the polynucleotide can be used in linkage analysis. Linkage analysis establishes coinheritance between a chromosomal location and presentation of a particular disease. (Disease mapping data are found, for example, in V. McKusick,

Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library).) Assuming 1 megabase mapping resolution and one gene per 20 kb, a cDNA precisely localized to a chromosomal region associated with the disease could be one of 50-500 potential causative genes.

[0274] Thus, once coinheritance is established, differences in a polynucleotide of the invention and the corresponding gene between affected and unaffected individuals can be examined. First, visible structural alterations in the chromosomes, such as deletions or translocations, are examined in chromosome spreads or by PCR. If no structural alterations exist, the presence of point mutations are ascertained. Mutations observed in some or all affected individuals, but not in normal individuals, indicates that the mutation may cause the disease. However, complete sequencing of the polypeptide and the corresponding gene from several normal individuals is required to distinguish the mutation from a polymorphism. If a new polymorphism is identified, this polymorphic polypeptide can be used for further linkage analysis.

[0275] Furthermore, increased or decreased expression of the gene in affected individuals as compared to unaffected individuals can be assessed using the polynucleotides of the invention. Any of these alterations (altered expression, chromosomal rearrangement, or mutation) can be used as a diagnostic or prognostic marker.

[0276] Thus, the invention provides a method of detecting increased or decreased expression levels of the prostate cancer polynucleotides in affected individuals as compared to unaffected individuals using polynucleotides of the present invention and techniques known in the art, including but not limited to the method described in Example 11. Any of these alterations (altered expression, chromosomal rearrangement, or mutation) can be used as a diagnostic or prognostic marker.

[0277] Thus, the invention also provides a diagnostic method useful during diagnosis of a prostate related disorder, including prostate cancer, involving measuring the expression level of prostate cancer polynucleotides in prostate tissue or other cells or body fluid from an individual and comparing the measured gene expression level with a standard prostate cancer polynucleotide expression level, whereby an increase or decrease in the gene expression level compared to the standard is indicative of a prostate related disorder.

[0278] In still another embodiment, the invention includes a kit for analyzing samples for the presence of proliferative and/or cancerous polynucleotides derived from a test subject. In a general embodiment, the kit includes at least one polynucleotide probe containing a nucleotide sequence that will specifically hybridize with a polynucleotide of the invention and a suitable container. In a specific embodiment, the kit includes two polynucleotide probes defining an internal region of the polynucleotide of the invention, where each probe has one strand containing a 31'mer-end internal to the region. In a further embodiment, the probes may be useful as primers for polymerase chain reaction amplification.

[0279] Where a diagnosis of a prostate related disorder, including, for example, diagnosis of a tumor, has already been made according to conventional methods, the present invention is useful as a prognostic indicator, whereby patients exhibiting enhanced or depressed prostate cancer polynucleotide expression will experience a worse clinical outcome relative to patients expressing the gene at a level nearer the standard level.

[0280] By "measuring the expression level of prostate cancer polynucleotides" is intended qualitatively or quantitatively measuring or estimating the level of the prostate cancer polypeptide or the level of the mRNA encoding the prostate cancer polypeptide in a first biological sample either directly (e.g., by determining or estimating absolute protein level or mRNA level) or relatively (e.g., by comparing to the prostate cancer polypeptide level or mRNA level in a second biological sample). Preferably, the prostate cancer polypeptide level or mRNA level in the first biological sample is measured or estimated and compared to a standard prostate cancer polypeptide level or mRNA level, the standard being taken from a second biological sample obtained from an individual not having the prostate related disorder or being determined by averaging levels from a population of individuals not having a prostate related disorder. As will be appreciated in the art, once a standard prostate cancer polypeptide level or mRNA level is known, it can be used repeatedly as a standard for comparison.

[0281] By "biological sample" is intended any biological sample obtained from an individual, body fluid, cell line, tissue culture, or other source which contains prostate cancer polypeptide or the corresponding mRNA. As indicated, biological samples include body fluids (such as semen, lymph, sera, plasma, urine, synovial fluid and spinal fluid) which contain the prostate cancer polypeptide, prostate tissue, and other tissue sources

found to express the prostate cancer polypeptide. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred source.

[0282] The method(s) provided above may preferrably be applied in a diagnostic method and/or kits in which polynucleotides and/or polypeptides of the invention are attached to a solid support. In one exemplary method, the support may be a "gene chip" or a "biological chip" as described in US Patents 5,837,832, 5,874,219, and 5,856,174. Further, such a gene chip with prostate cancer polynucleotides attached may be used to identify polymorphisms between the prostate cancer polynucleotide sequences, with polynucleotides isolated from a test subject. The knowledge of such polymorphisms (i.e. their location, as well as, their existence) would be beneficial in identifying disease loci for many disorders, such as for example, in neural disorders, immune system disorders, muscular disorders, reproductive disorders, gastrointestinal disorders, pulmonary disorders, cardiovascular disorders, renal disorders, proliferative disorders, and/or cancerous diseases and conditions, though most preferably in prostate related proliferative, and/or cancerous diseases and conditions. Such a method is described in US Patents 5,858,659 and 5,856,104. The US Patents referenced supra are hereby incorporated by reference in their entirety herein.

[0283] The present invention encompasses prostate cancer polynucleotides that are chemically synthesized, or reproduced as peptide nucleic acids (PNA), or according to other methods known in the art. The use of PNAs would serve as the preferred form if the polynucleotides of the invention are incorporated onto a solid support, or gene chip. For the purposes of the present invention, a peptide nucleic acid (PNA) is a polyamide type of DNA analog and the monomeric units for adenine, guanine, thymine and cytosine are available commercially (Perceptive Biosystems). Certain components of DNA, such as phosphorus, phosphorus oxides, or deoxyribose derivatives, are not present in PNAs. As disclosed by P. E. Nielsen, M. Egholm, R. H. Berg and O. Buchardt, Science 254, 1497 (1991); and M. Egholm, O. Buchardt, L.Christensen, C. Behrens, S. M. Freier, D. A. Driver, R. H. Berg, S. K. Kim, B. Norden, and P. E. Nielsen, Nature 365, 666 (1993), PNAs bind specifically and tightly to complementary DNA strands and are not degraded by nucleases. In fact, PNA binds more strongly to DNA than DNA itself does. This is probably because there is no electrostatic repulsion between the two strands, and also the

polyamide backbone is more flexible. Because of this, PNA/DNA duplexes bind under a wider range of stringency conditions than DNA/DNA duplexes, making it easier to perform multiplex hybridization. Smaller probes can be used than with DNA due to the strong binding. In addition, it is more likely that single base mismatches can be determined with PNA/DNA hybridization because a single mismatch in a PNA/DNA 15-mer lowers the melting point (T.sub.m) by 8°-20° C, vs. 4°-16° C for the DNA/DNA 15-mer duplex. Also, the absence of charge groups in PNA means that hybridization can be done at low ionic strengths and reduce possible interference by salt during the analysis.

[0284] The present invention have uses which include, but are not limited to, detecting cancer in mammals. In particular the invention is useful during diagnosis of pathological cell proliferative neoplasias which include, but are not limited to: acute myelogenous leukemias including acute monocytic leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute erythroleukemia, acute megakaryocytic leukemia, and acute undifferentiated leukemia, etc.; and chronic myelogenous leukemias including chronic myelomonocytic leukemia, chronic granulocytic leukemia, etc. Preferred mammals include monkeys, apes, cats, dogs, cows, pigs, horses, rabbits and humans. Particularly preferred are humans.

[0285] Pathological cell proliferative disorders are often associated with inappropriate activation of proto-oncogenes. (Gelmann, E. P. et al., "The Etiology of Acute Leukemia: Molecular Genetics and Viral Oncology," in Neoplastic Diseases of the Blood, Vol 1., Wiernik, P. H. et al. eds., 161-182 (1985)). Neoplasias are now believed to result from the qualitative alteration of a normal cellular gene product, or from the quantitative modification of gene expression by insertion into the chromosome of a viral sequence, by chromosomal translocation of a gene to a more actively transcribed region, or by some other mechanism. (Gelmann et al., supra) It is likely that mutated or altered expression of specific genes is involved in the pathogenesis of some leukemias, among other tissues and cell types. (Gelmann et al., supra) Indeed, the human counterparts of the oncogenes involved in some animal neoplasias have been amplified or translocated in some cases of human leukemia and carcinoma. (Gelmann et al., supra)

[0286] For example, c-myc expression is highly amplified in the non-lymphocytic leukemia cell line HL-60. When HL-60 cells are chemically induced to stop proliferation, the level of c-myc is found to be downregulated. (International Publication Number WO

91/15580). However, it has been shown that exposure of HL-60 cells to a DNA construct that is complementary to the 5' end of c-myc or c-myb blocks translation of the corresponding mRNAs which downregulates expression of the c-myc or c-myb proteins and causes arrest of cell proliferation and differentiation of the treated cells. (International Publication Number WO 91/15580; Wickstrom et al., Proc. Natl. Acad. Sci. 85:1028 (1988); Anfossi et al., Proc. Natl. Acad. Sci. 86:3379 (1989)). However, the skilled artisan would appreciate the present invention's usefulness is not limited to treatment of proliferative disorders of hematopoietic cells and tissues, in light of the numerous cells and cell types of varying origins which are known to exhibit proliferative phenotypes.

[0287] In addition to the foregoing, a prostate cancer antigen polynucleotide can be used to control gene expression through triple helix formation or through antisense DNA or RNA. Antisense techniques are discussed, for example, in Okano, J. Neurochem. 56: 560 (1991); "Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance Lee et al., Nucleic Acids Research 6: 3073 (1979); Cooney et al., Science 241: 456 (1988); and Dervan et al., Science 251: 1360 (1991). Both methods rely on binding of the polynucleotide to a complementary DNA or RNA. For these techniques, preferred polynucleotides are usually oligonucleotides 20 to 40 bases in length and complementary to either the region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res. 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1360 (1991)) or to the mRNA itself (antisense - Okano, J. Neurochem. 56:560 (1991); Oligodeoxy-nucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988).) Triple helix formation optimally results in a shut-off of RNA transcription from DNA, while antisense RNA hybridization blocks translation of an mRNA molecule into polypeptide. The oligonucleotide described above can also be delivered to cells such that the antisense RNA or DNA may be expressed in vivo to inhibit production of polypeptide of the present invention antigens. Both techniques are effective in model systems, and the information disclosed herein can be used to design antisense or triple helix polynucleotides in an effort to treat disease, and in particular, for the treatment of proliferative diseases and/or conditions.

[0288] Polynucleotides of the present invention are also useful in gene therapy. One goal of gene therapy is to insert a normal gene into an organism having a defective

gene, in an effort to correct the genetic defect. The polynucleotides disclosed in the present invention offer a means of targeting such genetic defects in a highly accurate manner. Another goal is to insert a new gene that was not present in the host genome, thereby producing a new trait in the host cell.

[0289] The polynucleotides are also useful for identifying individuals from minute biological samples. The United States military, for example, is considering the use of restriction fragment length polymorphism (RFLP) for identification of its personnel. In this technique, an individual's genomic DNA is digested with one or more restriction enzymes, and probed on a Southern blot to yield unique bands for identifying personnel. This method does not suffer from the current limitations of "Dog Tags" which can be lost, switched, or stolen, making positive identification difficult. The polynucleotides of the present invention can be used as additional DNA markers for RFLP.

[0290] The polynucleotides of the present invention can also be used as an alternative to RFLP, by determining the actual base-by-base DNA sequence of selected portions of an individual's genome. These sequences can be used to prepare PCR primers for amplifying and isolating such selected DNA, which can then be sequenced. Using this technique, individuals can be identified because each individual will have a unique set of DNA sequences. Once an unique ID database is established for an individual, positive identification of that individual, living or dead, can be made from extremely small tissue samples.

[0291] Forensic biology also benefits from using DNA-based identification techniques as disclosed herein. DNA sequences taken from very small biological samples such as tissues, e.g., hair or skin, or body fluids, e.g., blood, saliva, semen, synovial fluid, amniotic fluid, breast milk, lymph, pulmonary sputum or surfactant, urine, fecal matter, etc., can be amplified using PCR. In one prior art technique, gene sequences amplified from polymorphic loci, such as DQa class II HLA gene, are used in forensic biology to identify individuals. (Erlich, H., PCR Technology, Freeman and Co. (1992).) Once these specific polymorphic loci are amplified, they are digested with one or more restriction enzymes, yielding an identifying set of bands on a Southern blot probed with DNA corresponding to the DQa class II HLA gene. Similarly, polynucleotides of the present invention can be used as polymorphic markers for forensic purposes.

[0292] There is also a need for reagents capable of identifying the source of a particular tissue. Such need arises, for example, in forensics when presented with tissue of unknown origin. Appropriate reagents can comprise, for example, DNA probes or primers specific to prostate or prostate cancer polynucleotides prepared from the sequences of the present invention. Panels of such reagents can identify tissue by species and/or by organ type. In a similar fashion, these reagents can be used to screen tissue cultures for contamination.

[0293] The polynucleotides of the present invention are also useful as hybridization probes for differential identification of the tissue(s) or cell type(s) present in a biological sample. Similarly, polypeptides and antibodies directed to polypeptides of the present invention are useful to provide immunological probes for differential identification of the tissue(s) (e.g., immunohistochemistry assays) or cell type(s) (e.g., immunocytochemistry assays). In addition, for a number of disorders of the above tissues or cells, significantly higher or lower levels of gene expression of the polynucleotides/polypeptides of the present invention may be detected in certain tissues (e.g., tissues expressing polypeptides and/or polynucleotides of the present invention, prostate and prostate cancer tissues and/or cancerous and/or wounded tissues) or bodily fluids (e.g., serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to a "standard" gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

[0294] Thus, the invention provides a diagnostic method of a disorder, which involves: (a) assaying gene expression level in cells or body fluid of an individual; (b) comparing the gene expression level with a standard gene expression level, whereby an increase or decrease in the assayed gene expression level compared to the standard expression level is indicative of a disorder.

[0295] In the very least, the polynucleotides of the present invention can be used as molecular weight markers on Southern gels, as diagnostic probes for the presence of a specific mRNA in a particular cell type, as a probe to "subtract-out" known sequences in the process of discovering novel polynucleotides, for selecting and making oligomers for attachment to a "gene chip" or other support, to raise anti-DNA antibodies using DNA immunization techniques, and as an antigen to elicit an immune response.

Uses of the Polypeptides

[0296] Each of the polypeptides identified herein can be used in numerous ways. The following description should be considered exemplary and utilizes known techniques.

[0297] Polypeptides and antibodies directed to polypeptides of the present invention are useful to provide immunological probes for differential identification of the tissue(s) (e.g., immunohistochemistry assays such as, for example, ABC immunoperoxidase (Hsu et al., J. Histochem. Cytochem. 29:577-580 (1981)) or cell type(s) (e.g., immunocytochemistry assays).

[0298] Antibodies can be used to assay levels of polypeptides encoded by polynucleotides of the invention in a biological sample using classical immunohistological methods known to those of skill in the art (e.g., see Jalkanen, et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, et al., J. Cell. Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine (^{131}I, ^{125}I, ^{123}I, ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium (^{115m}In, ^{113m}In, ^{112}In, ^{111}In), and technetium (^{99}Tc, ^{99m}Tc), thallium (^{201}Ti), gallium (^{68}Ga, ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F), ^{153}Sm, ^{177}Lu, ^{159}Gd, ^{149}Pm, ^{140}La, ^{175}Yb, ^{166}Ho, ^{90}Y, ^{47}Sc, ^{186}Re, ^{188}Re, ^{142}Pr, ^{105}Rh, ^{97}Ru; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[0299] In addition to assaying levels of polypeptide of the present invention in a biological sample, proteins can also be detected in vivo by imaging. Antibody labels or markers for in vivo imaging of protein include those detectable by X-radiography, NMR or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the antibody by labeling of nutrients for the relevant hybridoma.

[0300] A protein-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example, ^{131}I, ^{112}In, ^{99m}Tc, (^{131}I, ^{125}I, ^{123}I, ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium (^{115m}In,

^{113m}In, ^{112}In, ^{111}In), and technetium (^{99}Tc, ^{99m}Tc), thallium (^{201}Ti), gallium (^{68}Ga, ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F, ^{153}Sm, ^{177}Lu, ^{159}Gd, ^{149}Pm, ^{140}La, ^{175}Yb, ^{166}Ho, ^{90}Y, ^{47}Sc, ^{186}Re, ^{188}Re, ^{142}Pr, ^{105}Rh, ^{97}Ru), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously or intraperitoneally) into the mammal to be examined for immune system disorder. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of ^{99m}Tc. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which express the polypeptide encoded by a polynucleotide of the invention. *In vivo* tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments" (Chapter 13 in *Tumor Imaging: The Radiochemical Detection of Cancer*, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)).

[0301] In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells by administering polypeptides of the invention (e.g., polypeptides encoded by polynucleotides of the invention and/or antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

[0302] In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention in association with toxins or cytotoxic prodrugs.

[0303] In a preferred embodiment, the invention provides a method for the specific destruction of prostate cells (e.g., aberrant prostate cells, prostate neoplasm) by administering polypeptides of the invention (e.g., polypeptides encoded by polynucleotides of the invention and/or antibodies) in association with toxins or cytotoxic prodrugs.

[0304] By "toxin" is meant one or more compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNAse, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. "Toxin" also includes a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, ^{213}Bi, or other radioisotopes such as, for example, ^{103}Pd, ^{133}Xe, ^{131}I, ^{68}Ge, ^{57}Co, ^{65}Zn, ^{85}Sr, ^{32}P, ^{35}S, ^{90}Y, ^{153}Sm, ^{153}Gd, ^{169}Yb, ^{51}Cr, ^{54}Mn, ^{75}Se, ^{113}Sn, ^{90}Yttrium, ^{117}Tin, ^{186}Rhenium, ^{166}Holmium, and ^{188}Rhenium; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[0305] In a specific embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention or antibodies of the invention in association with the radioisotope ^{90}Y. In another specific embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention or antibodies of the invention in association with the radioisotope ^{111}In. In a further specific embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention or antibodies of the invention in association with the radioisotope ^{131}I.

[0306] Techniques known in the art may be applied to label polypeptides of the invention (including antibodies). Such techniques include, but are not limited to, the use of bifunctional conjugating agents (see e.g., U.S. Patent Nos. 5,756,065; 5,714,631; 5,696,239; 5,652,361; 5,505,931; 5,489,425; 5,435,990; 5,428,139; 5,342,604; 5,274,119; 4,994,560; and 5,808,003; the contents of each of which are hereby incorporated by reference in its entirety).

[0307] Thus, the invention provides a diagnostic method of a disorder, which involves (a) assaying the expression level of a prostate cancer polypeptide of the present

invention in cells or body fluid of an individual, or more preferrably, assaying the expression level of a prostate cancer polypeptide of the present invention in prostate cells or semen of an individual; and (b) comparing the assayed polypeptide expression level with a standard polypeptide expression level, whereby an increase or decrease in the assayed polypeptide expression level compared to the standard expression level is indicative of a disorder. With respect to cancer, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

[0308] Moreover, prostate cancer antigen polypeptides of the present invention can be used to treat or prevent diseases or conditions such as, for example, neural disorders, immune system disorders, muscular disorders, reproductive disorders, gastrointestinal disorders, pulmonary disorders, cardiovascular disorders, renal disorders, proliferative disorders, and/or cancerous diseases and conditions, preferably proliferative disorders of the prostate, and/or cancerous disease and conditions. Preferably, polypeptides of the present invention can be used to treat or prevent diseases or conditions of the prostate such as, for example, prostate cancers such as adenocarcinoma, transitional cell carcinomas, ductal carcinomas, and squamous cell carcinomas, and as described under "Hyperproliferative Disorders" and/or "Reproductive System Disorders" below. For example, patients can be administered a polypeptide of the present invention in an effort to replace absent or decreased levels of the polypeptide (e.g., insulin), to supplement absent or decreased levels of a different polypeptide (e.g., hemoglobin S for hemoglobin B, SOD, catalase, DNA repair proteins), to inhibit the activity of a polypeptide (e.g., an oncogene or tumor supressor), to activate the activity of a polypeptide (e.g., by binding to a receptor), to reduce the activity of a membrane bound receptor by competing with it for free ligand (e.g., soluble TNF receptors used in reducing inflammation), or to bring about a desired response (e.g., blood vessel growth inhibition, enhancement of the immune response to proliferative cells or tissues).

[0309] Similarly, antibodies directed to a polypeptide of the present invention can also be used to treat disease (as described *supra*, and elsewhere herein). For example,

administration of an antibody directed to a polypeptide of the present invention can bind, and/or neutralize the polypeptide, and/or reduce overproduction of the polypeptide. Similarly, administration of an antibody can activate the polypeptide, such as by binding to a polypeptide bound to a membrane (receptor).

[0310] At the very least, the polypeptides of the present invention can be used as molecular weight markers on SDS-PAGE gels or on molecular sieve gel filtration columns using methods well known to those of skill in the art. Polypeptides can also be used to raise antibodies, which in turn are used to measure protein expression from a recombinant cell, as a way of assessing transformation of the host cell. Moreover, the polypeptides of the present invention can be used to test the following biological activities.

Diagnostic Asssays

[0311] The compounds of the present invention are useful for diagnosis, treatment, prevention and/or prognosis of various prostate-related disorders in mammals, preferably humans. Such disorders include, but are not limited to, prostate cancers such as adenocarcinoma, transitional cell carcinomas, ductal carcinomas, and squamous cell carcinomas, and as described under "Hyperproliferative Disorders" and/or "Reproductive System Disorders" below.

[0312] Prostate cancer antigens are expressed in the prostate. For a number of prostate-related disorders, substantially altered (increased or decreased) levels of prostate cancer antigen gene expression can be detected in prostate cancer tissue or other cells or bodily fluids (e.g., sera, plasma, urine, semen, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to a "standard" prostate cancer antigen gene expression level, that is, the prostate cancer antigen expression level in prostate tissues or bodily fluids from an individual not having the prostate disorder. Thus, the invention provides a diagnostic method useful during diagnosis of a prostate disorder, which involves measuring the expression level of the gene encoding the prostate cancer associated polypeptide in prostate tissue or other cells or body fluid from an individual and comparing the measured gene expression level with a standard prostate cancer antigens gene expression level, whereby an increase or decrease in the gene expression level(s) compared to the standard is indicative of an prostate disorder.

[0313] In specific embodiments, the invention provides a diagnostic method useful

during diagnosis of a disorder of a normal or diseased tissue/cell source, which involves measuring the expression level of the coding sequence of a polynucleotide sequence associated with this tissue/cell source as disclosed by Tables 1 and 5 in the tissue/cell source or other cells or body fluid from an individual and comparing the expression level of the coding sequence with a standard expression level of the coding sequence of a polynucleotide sequence, whereby an increase or decrease in the gene expression level(s) compared to the standard is indicative of a disorder of a normal or diseased tissue/cell source.

[0314] In particular, it is believed that certain tissues in mammals with cancer of cells or tissue of the prostate express significantly enhanced or reduced levels of normal or altered prostate cancer antigen expression and mRNA encoding the prostate cancer associated polypeptide when compared to a corresponding "standard" level. Further, it is believed that enhanced or depressed levels of the prostate cancer associated polypeptide can be detected in certain body fluids (e.g., sera, plasma, urine, and spinal fluid) or cells or tissue from mammals with such a cancer when compared to sera from mammals of the same species not having the cancer.

[0315] For example, as disclosed herein, prostate cancer associated polypeptides of the invention are expressed in the prostate. Accordingly, polynucleotides of the invention (e.g., polynucleotide sequences complementary to all or a portion of a prostate cancer antigen mRNA nucleotide sequence of SEQ ID NO:X, the nucleotide coding sequence of the related cDNA contained in a deposited library, a nucleotide sequence encoding SEQ ID NO:Y, a nucleotide sequence encoding a polypeptide encoded by SEQ ID NO:X, the nucleotide sequence encoding the polypeptide encoded by the cDNA in the related cDNA contained in a deposited library, polynucleotide fragments of any of these nucleic acid molecules (e.g., those fragments described herein), and/or antibodies (and antibody fragments) directed against the polypeptides of the invention may be used to quantitate or qualitate concentrations of cells of the prostate cancer expressing prostate cancer antigens, preferrably on their cell surfaces. These polynucleotides and antibodies additionally have diagnostic applications in detecting abnormalities in the level of prostate cancer antigens gene expression, or abnormalities in the structure and/or temporal, tissue, cellular, or subcellular location of prostate cancer antigens. These diagnostic assays may be performed *in vivo* or *in vitro*, such as, for example, on blood samples, biopsy tissue or

autopsy tissue.

[0316] Thus, the invention provides a diagnostic method useful during diagnosis of a prostate disorder, including cancers, which involves measuring the expression level of the gene encoding the prostate cancer antigen polypeptide in prostate tissue or other cells or body fluid from an individual and comparing the measured gene expression level with a standard prostate cancer antigen gene expression level, whereby an increase or decrease in the gene expression level compared to the standard is indicative of a prostate disorder.

[0317] Where a diagnosis of a disorder in the prostate, including diagnosis of a tumor, has already been made according to conventional methods, the present invention is useful as a prognostic indicator, whereby patients exhibiting enhanced or depressed prostate cancer antigen gene expression will experience a worse clinical outcome relative to patients expressing the gene at a level nearer the standard level.

[0318] By "assaying the expression level of the gene encoding the prostate cancer associated polypeptide" is intended qualitatively or quantitatively measuring or estimating the level of the prostate cancer antigen polypeptide or the level of the mRNA encoding the prostate cancer antigen polypeptide in a first biological sample either directly (e.g., by determining or estimating absolute protein level or mRNA level) or relatively (e.g., by comparing to the prostate cancer associated polypeptide level or mRNA level in a second biological sample). Preferably, the prostate cancer antigen polypeptide expression level or mRNA level in the first biological sample is measured or estimated and compared to a standard prostate cancer antigen polypeptide level or mRNA level, the standard being taken from a second biological sample obtained from an individual not having the disorder or being determined by averaging levels from a population of individuals not having a disorder of the prostate. As will be appreciated in the art, once a standard prostate cancer antigen polypeptide level or mRNA level is known, it can be used repeatedly as a standard for comparison.

[0319] By "biological sample" is intended any biological sample obtained from an individual, cell line, tissue culture, or other source containing prostate cancer antigen polypeptides (including portions thereof) or mRNA. As indicated, biological samples include body fluids (such as sera, plasma, urine, synovial fluid and spinal fluid) which contain cells expressing prostate cancer antigen polypeptides, prostate tissue, and other tissue sources found to express the full length or fragments thereof of a prostate cancer

antigen. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred source.

[0320] Total cellular RNA can be isolated from a biological sample using any suitable technique such as the single-step guanidinium-thiocyanate-phenol-chloroform method described in Chomczynski and Sacchi, Anal. Biochem. 162:156-159 (1987). Levels of mRNA encoding the prostate cancer antigen polypeptides are then assayed using any appropriate method. These include Northern blot analysis, S1 nuclease mapping, the polymerase chain reaction (PCR), reverse transcription in combination with the polymerase chain reaction (RT-PCR), and reverse transcription in combination with the ligase chain reaction (RT-LCR).

[0321] The present invention also relates to diagnostic assays such as quantitative and diagnostic assays for detecting levels of prostate cancer antigen polypeptides, in a biological sample (e.g., cells and tissues), including determination of normal and abnormal levels of polypeptides. Thus, for instance, a diagnostic assay in accordance with the invention for detecting over-expression of prostate cancer antigens compared to normal control tissue samples may be used to detect the presence of tumors. Assay techniques that can be used to determine levels of a polypeptide, such as a prostate cancer antigen polypeptide of the present invention in a sample derived from a host are well-known to those of skill in the art. Such assay methods include radioimmunoassays, competitive-binding assays, Western Blot analysis and ELISA assays. Assaying prostate cancer antigen polypeptide levels in a biological sample can occur using any art-known method.

[0322] Assaying prostate cancer antigen polypeptide levels in a biological sample can occur using antibody-based techniques. For example, prostate cancer antigen polypeptide expression in tissues can be studied with classical immunohistological methods (Jalkanen et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, M., et al., J. Cell . Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting prostate cancer antigen polypeptide gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase, and radioisotopes, such as iodine (^{125}I, ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^{3}H), indium (^{112}In), and technetium (^{99m}Tc), and fluorescent labels, such as fluorescein

and rhodamine, and biotin.

[0323] The tissue or cell type to be analyzed will generally include those which are known, or suspected, to express the prostate cancer antigen gene (such as, for example, cells of the prostate or prostate cancer). The protein isolation methods employed herein may, for example, be such as those described in Harlow and Lane (Harlow, E. and Lane, D., 1988, "Antibodies: A Laboratory Manual", Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York), which is incorporated herein by reference in its entirety. The isolated cells can be derived from cell culture or from a patient. The analysis of cells taken from culture may be a necessary step in the assessment of cells that could be used as part of a cell-based gene therapy technique or, alternatively, to test the effect of compounds on the expression of the prostate cancer antigen gene.

[0324] For example, antibodies, or fragments of antibodies, such as those described herein, may be used to quantitatively or qualitatively detect the presence of prostate cancer antigen gene products or conserved variants or peptide fragments thereof. This can be accomplished, for example, by immunofluorescence techniques employing a fluorescently labeled antibody coupled with light microscopic, flow cytometric, or fluorimetric detection.

[0325] In a preferred embodiment, antibodies, or fragments of antibodies directed to any one or all of the predicted epitope domains of the prostate cancer antigen polypeptides (Shown in Table 4) may be used to quantitatively or qualitatively detect the presence of prostate cancer antigen gene products or conserved variants or peptide fragments thereof. This can be accomplished, for example, by immunofluorescence techniques employing a fluorescently labeled antibody coupled with light microscopic, flow cytometric, or fluorimetric detection.

[0326] In an additional preferred embodiment, antibodies, or fragments of antibodies directed to a conformational epitope of a prostate cancer antigen may be used to quantitatively or qualitatively detect the presence of prostate cancer antigen gene products or conserved variants or peptide fragments thereof. This can be accomplished, for example, by immunofluorescence techniques employing a fluorescently labeled antibody coupled with light microscopic, flow cytometric, or fluorimetric detection.

[0327] The antibodies (or fragments thereof), and/or prostate cancer antigen polypeptides of the present invention may, additionally, be employed histologically, as in

immunofluorescence, immunoelectron microscopy or non-immunological assays, for in situ detection of prostate cancer antigen gene products or conserved variants or peptide fragments thereof. In situ detection may be accomplished by removing a histological specimen from a patient, and applying thereto a labeled antibody or prostate cancer antigen polypeptide of the present invention. The antibody (or fragment thereof) or prostate cancer antigen polypeptide is preferably applied by overlaying the labeled antibody (or fragment) onto a biological sample. Through the use of such a procedure, it is possible to determine not only the presence of the prostate cancer antigen gene product, or conserved variants or peptide fragments, or prostate cancer antigen polypeptide binding, but also its distribution in the examined tissue. Using the present invention, those of ordinary skill will readily perceive that any of a wide variety of histological methods (such as staining procedures) can be modified in order to achieve such in situ detection.

[0328] Immunoassays and non-immunoassays for prostate cancer antigen gene products or conserved variants or peptide fragments thereof will typically comprise incubating a sample, such as a biological fluid, a tissue extract, freshly harvested cells, or lysates of cells which have been incubated in cell culture, in the presence of a detectably labeled antibody capable of binding prostate cancer antigen gene products or conserved variants or peptide fragments thereof, and detecting the bound antibody by any of a number of techniques well-known in the art.

[0329] The biological sample may be brought in contact with and immobilized onto a solid phase support or carrier such as nitrocellulose, or other solid support which is capable of immobilizing cells, cell particles or soluble proteins. The support may then be washed with suitable buffers followed by treatment with the detectably labeled anti-prostate cancer antigen antibody or detectable prostate cancer antigen polypeptide. The solid phase support may then be washed with the buffer a second time to remove unbound antibody or polypeptide. Optionally the antibody is subsequently labeled. The amount of bound label on solid support may then be detected by conventional means.

[0330] By "solid phase support or carrier" is intended any support capable of binding an antigen or an antibody. Well-known supports or carriers include glass, polystyrene, polypropylene, polyethylene, dextran, nylon, amylases, natural and modified celluloses, polyacrylamides, gabbros, and magnetite. The nature of the carrier can be either soluble to some extent or insoluble for the purposes of the present invention. The

support material may have virtually any possible structural configuration so long as the coupled molecule is capable of binding to an antigen or antibody. Thus, the support configuration may be spherical, as in a bead, or cylindrical, as in the inside surface of a test tube, or the external surface of a rod. Alternatively, the surface may be flat such as a sheet, test strip, etc. Preferred supports include polystyrene beads. Those skilled in the art will know many other suitable carriers for binding antibody or antigen, or will be able to ascertain the same by use of routine experimentation.

[0331] The binding activity of a given lot of anti- prostate cancer antigen antibody or prostate cancer antigen polypeptide may be determined according to well known methods. Those skilled in the art will be able to determine operative and optimal assay conditions for each determination by employing routine experimentation.

[0332] In addition to assaying prostate cancer antigen polypeptide levels or polynucleotide levels in a biological sample obtained from an individual, prostate cancer antigen polypeptide or polynucleotide can also be detected *in vivo* by imaging. For example, in one embodiment of the invention, prostate cancer antigen polypeptide and/or anti- prostate cancer antigen antibodies are used to image prostate diseased cells, such as neoplasms. In another embodiment, prostate cancer antigen polynucleotides of the invention (e.g., polynucleotides complementary to all or a portion of prostate cancer antigen mRNA) and/or anti- prostate cancer antigen antibodies (e.g., antibodies directed to any one or a combination of the epitopes of prostate cancer antigens, antibodies directed to a conformational epitope of prostate cancer antigens, antibodies directed to the full length polypeptide expressed on the cell surface of a mammalian cell) are used to image diseased or neoplastic cells of the prostate.

[0333] Antibody labels or markers for *in vivo* imaging of prostate cancer antigen polypeptides include those detectable by X-radiography, NMR, MRI, CAT-scans or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the antibody by labeling of nutrients for the relevant hybridoma. Where *in vivo* imaging is used to detect enhanced levels of prostate cancer antigen polypeptides for diagnosis in humans, it may be preferable to use human antibodies or "humanized" chimeric monoclonal antibodies. Such antibodies can be

produced using techniques described herein or otherwise known in the art. For example methods for producing chimeric antibodies are known in the art. See, for review, Morrison, *Science 229*:1202 (1985); Oi et al., *BioTechniques 4*:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne *et al., Nature 312*:643 (1984); Neuberger *et al., Nature 314*:268 (1985).

[0334] Additionally, any prostate cancer antigen polypeptides whose presence can be detected, can be administered. For example, prostate cancer antigen polypeptides labeled with a radio-opaque or other appropriate compound can be administered and visualized *in vivo*, as discussed, above for labeled antibodies. Further such prostate cancer antigen polypeptides can be utilized for *in vitro* diagnostic procedures.

[0335] A prostate cancer antigen polypeptide-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example, ^{131}I, ^{112}In, ^{99m}Tc), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously or intraperitoneally) into the mammal to be examined for a prostate disorder. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of ^{99m}Tc. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain prostate cancer antigen protein. *In vivo* tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments" (Chapter 13 in *Tumor Imaging: The Radiochemical Detection of Cancer*, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)).

[0336] With respect to antibodies, one of the ways in which the anti- prostate cancer antigen antibody can be detectably labeled is by linking the same to an enzyme and using the linked product in an enzyme immunoassay (EIA) (Voller, A., "The Enzyme Linked Immunosorbent Assay (ELISA)", 1978, Diagnostic Horizons 2:1-7, Microbiological Associates Quarterly Publication, Walkersville, MD); Voller et al., *J. Clin. Pathol.* 31:507-520 (1978); Butler, J.E., *Meth. Enzymol.* 73:482-523 (1981); Maggio, E. (ed.), 1980, Enzyme Immunoassay, CRC Press, Boca Raton, FL,; Ishikawa, E.

et al., (eds.), 1981, Enzyme Immunoassay, Kgaku Shoin, Tokyo). The enzyme, which is bound to the antibody will react with an appropriate substrate, preferably a chromogenic substrate, in such a manner as to produce a chemical moiety which can be detected, for example, by spectrophotometric, fluorimetric or by visual means. Enzymes which can be used to detectably label the antibody include, but are not limited to, malate dehydrogenase, staphylococcal nuclease, delta-5-steroid isomerase, yeast alcohol dehydrogenase, alpha-glycerophosphate, dehydrogenase, triose phosphate isomerase, horseradish peroxidase, alkaline phosphatase, asparaginase, glucose oxidase, beta-galactosidase, ribonuclease, urease, catalase, glucose-6-phosphate dehydrogenase, glucoamylase and acetylcholinesterase. Additionally, the detection can be accomplished by colorimetric methods which employ a chromogenic substrate for the enzyme. Detection may also be accomplished by visual comparison of the extent of enzymatic reaction of a substrate in comparison with similarly prepared standards.

[0337] Detection may also be accomplished using any of a variety of other immunoassays. For example, by radioactively labeling the antibodies or antibody fragments, it is possible to detect prostate cancer antigens through the use of a radioimmunoassay (RIA) (see, for example, Weintraub, B., Principles of Radioimmunoassays, Seventh Training Course on Radioligand Assay Techniques, The Endocrine Society, March, 1986, which is incorporated by reference herein). The radioactive isotope can be detected by means including, but not limited to, a gamma counter, a scintillation counter, or autoradiography.

[0338] It is also possible to label the antibody with a fluorescent compound. When the fluorescently labeled antibody is exposed to light of the proper wave length, its presence can then be detected due to fluorescence. Among the most commonly used fluorescent labeling compounds are fluorescein isothiocyanate, rhodamine, phycoerythrin, phycocyanin, allophycocyanin, ophthaldehyde and fluorescamine.

[0339] The antibody can also be detectably labeled using fluorescence emitting metals such as ^{152}Eu, or others of the lanthanide series. These metals can be attached to the antibody using such metal chelating groups as diethylenetriaminepentacetic acid (DTPA) or ethylenediaminetetraacetic acid (EDTA).

[0340] The antibody also can be detectably labeled by coupling it to a chemiluminescent compound. The presence of the chemiluminescent-tagged antibody is

then determined by detecting the presence of luminescence that arises during the course of a chemical reaction. Examples of particularly useful chemiluminescent labeling compounds are luminol, isoluminol, theromatic acridinium ester, imidazole, acridinium salt and oxalate ester.

[0341] Likewise, a bioluminescent compound may be used to label the antibody of the present invention. Bioluminescence is a type of chemiluminescence found in biological systems in, which a catalytic protein increases the efficiency of the chemiluminescent reaction. The presence of a bioluminescent protein is determined by detecting the presence of luminescence. Important bioluminescent compounds for purposes of labeling are luciferin, luciferase and aequorin.

Methods for Detecting Prostate Disease, Including Cancer

[0342] In general, a prostate disease or cancer may be detected in a patient based on the presence of one or more prostate cancer antigen proteins of the invention and/or polynucleotides encoding such proteins in a biological sample (for example, blood, sera, urine, and/or tumor biopsies) obtained from the patient. In other words, such proteins and/or polynucleotides may be used as markers to indicate the presence or absence of a prostate disease or disorder, including cancer. Cancers that may be diagnosed, and/or prognosed using the compositions of the invention include but are not limited to, prostate cancer. The binding agents provided herein generally permit detection of the level of antigen that binds to the agent in the biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding prostate cancer antigen polypeptides, which is also indicative of the presence or absence of a prostate disease or disorder, including cancer. In general, prostate cancer antigen polypeptides should be present at a level that is at least three fold higher in diseased tissue than in normal tissue.

[0343] There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. See, e.g., Harlow and Lane, *supra.* In general, the presence or absence of a prostate disease in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

[0344] In a preferred embodiment, the assay involves the use of binding agent immobilized on a solid support to bind to and remove the prostate cancer antigen polypeptide of the invention from the remainder of the sample. The bound polypeptide may then be detected using a detection reagent that contains a reporter group and specifically binds to the binding agent/polypeptide complex. Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such assays include prostate cancer antigen polypeptides and portions thereof, or antibodies, to which the binding agent binds, as described above.

[0345] The solid support may be any material known to those of skill in the art to which prostate cancer antigen polypeptides of the invention may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for the suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of plastic microtiter plate (such as polystyrene or polyvinylchloride) with an

amount of binding agent ranging from about 10 ng to about 10 ug, and preferably about 100 ng to about 1 ug, is sufficient to immobilize an adequate amount of binding agent.

[0346] Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (see, e.g., Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

<u>Gene Therapy Methods</u>

[0347] Another aspect of the present invention is to gene therapy methods for treating or preventing disorders, diseases and conditions. The gene therapy methods relate to the introduction of nucleic acid (DNA, RNA and antisense DNA or RNA) sequences into an animal to achieve expression of the polypeptide of the present invention. This method requires a polynucleotide which codes for a polypeptide of the present invention operatively linked to a promoter and any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques are known in the art, see, for example, WO90/11092, which is herein incorporated by reference.

[0348] Thus, for example, cells from a patient may be engineered with a polynucleotide (DNA or RNA) comprising a promoter operably linked to a polynucleotide of the present invention ex vivo, with the engineered cells then being provided to a patient to be treated with the polypeptide of the present invention. Such methods are well-known in the art. For example, see Belldegrun, A., et al., J. Natl. Cancer Inst. 85: 207-216 (1993); Ferrantini, M. et al., Cancer Research 53: 1107-1112 (1993); Ferrantini, M. et al., J. Immunology 153: 4604-4615 (1994); Kaido, T., et al., Int. J. Cancer 60: 221-229 (1995); Ogura, H., et al., Cancer Research 50: 5102-5106 (1990); Santodonato, L., et al., Human Gene Therapy 7:1-10 (1996); Santodonato, L., et al., Gene Therapy 4:1246-1255 (1997); and Zhang, J.-F. et al., Cancer Gene Therapy 3: 31-38 (1996)), which are herein incorporated by reference. In one embodiment, the cells which are engineered are arterial

cells. The arterial cells may be reintroduced into the patient through direct injection to the artery, the tissues surrounding the artery, or through catheter injection.

[0349] As discussed in more detail below, the polynucleotide constructs can be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, and the like). The polynucleotide constructs may be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

[0350] In one embodiment, the polynucleotide of the present invention is delivered as a naked polynucleotide. The term "naked" polynucleotide, DNA or RNA refers to sequences that are free from any delivery vehicle that acts to assist, promote or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotide of the present invention can also be delivered in liposome formulations and lipofectin formulations and the like can be prepared by methods well known to those skilled in the art. Such methods are described, for example, in U.S. Patent Nos. 5,593,972, 5,589,466, and 5,580,859, which are herein incorporated by reference.

[0351] The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Appropriate vectors include pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; pSVK3, pBPV, pMSG and pSVL available from Pharmacia; and pEF1/V5, pcDNA3.1, and pRc/CMV2 available from Invitrogen. Other suitable vectors will be readily apparent to the skilled artisan.

[0352] Any strong promoter known to those skilled in the art can be used for driving the expression of the polynucleotide sequence. Suitable promoters include adenoviral promoters, such as the adenoviral major late promoter; or heterologous promoters, such as the cytomegalovirus (CMV) promoter; the respiratory syncytial virus (RSV) promoter; inducible promoters, such as the MMT promoter, the metallothionein promoter; heat shock promoters; the albumin promoter; the ApoAI promoter; human globin promoters; viral thymidine kinase promoters, such as the Herpes Simplex thymidine kinase promoter; retroviral LTRs; the b-actin promoter; and human growth hormone promoters. The promoter also may be the native promoter for the polynucleotide of the present invention.

[0353] Unlike other gene therapy techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

[0354] The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular, fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. In vivo muscle cells are particularly competent in their ability to take up and express polynucleotides.

[0355] For the naked nucleic acid sequence injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 mg/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration.

[0356] The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial

tissues, throat or mucous membranes of the nose. In addition, naked DNA constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

[0357] The naked polynucleotides are delivered by any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, and so-called "gene guns". These delivery methods are known in the art.

[0358] The constructs may also be delivered with delivery vehicles such as viral sequences, viral particles, liposome formulations, lipofectin, precipitating agents, etc. Such methods of delivery are known in the art.

[0359] In certain embodiments, the polynucleotide constructs are complexed in a liposome preparation. Liposomal preparations for use in the instant invention include cationic (positively charged), anionic (negatively charged) and neutral preparations. However, cationic liposomes are particularly preferred because a tight charge complex can be formed between the cationic liposome and the polyanionic nucleic acid. Cationic liposomes have been shown to mediate intracellular delivery of plasmid DNA (Felgner et al., Proc. Natl. Acad. Sci. USA (1987) 84:7413-7416, which is herein incorporated by reference); mRNA (Malone et al., Proc. Natl. Acad. Sci. USA (1989) 86:6077-6081, which is herein incorporated by reference); and purified transcription factors (Debs et al., J. Biol. Chem. (1990) 265:10189-10192, which is herein incorporated by reference), in functional form.

[0360] Cationic liposomes are readily available. For example, N[1-2,3-dioleyloxy)propyl]-N,N,N-triethylammonium (DOTMA) liposomes are particularly useful and are available under the trademark Lipofectin, from GIBCO BRL, Grand Island, N.Y. (See, also, Felgner et al., Proc. Natl Acad. Sci. USA (1987) 84:7413-7416, which is herein incorporated by reference). Other commercially available liposomes include transfectace (DDAB/DOPE) and DOTAP/DOPE (Boehringer).

[0361] Other cationic liposomes can be prepared from readily available materials using techniques well known in the art. See, e.g. PCT Publication No. WO 90/11092 (which is herein incorporated by reference) for a description of the synthesis of DOTAP (1,2-bis(oleoyloxy)-3-(trimethylammonio)propane) liposomes. Preparation of DOTMA liposomes is explained in the literature, see, e.g., P. Felgner et al., Proc. Natl. Acad. Sci.

USA 84:7413-7417, which is herein incorporated by reference. Similar methods can be used to prepare liposomes from other cationic lipid materials.

[0362] Similarly, anionic and neutral liposomes are readily available, such as from Avanti Polar Lipids (Birmingham, Ala.), or can be easily prepared using readily available materials. Such materials include phosphatidyl, choline, cholesterol, phosphatidyl ethanolamine, dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), dioleoylphoshatidyl ethanolamine (DOPE), among others. These materials can also be mixed with the DOTMA and DOTAP starting materials in appropriate ratios. Methods for making liposomes using these materials are well known in the art.

[0363] For example, commercially dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), and dioleoylphosphatidyl ethanolamine (DOPE) can be used in various combinations to make conventional liposomes, with or without the addition of cholesterol. Thus, for example, DOPG/DOPC vesicles can be prepared by drying 50 mg each of DOPG and DOPC under a stream of nitrogen gas into a sonication vial. The sample is placed under a vacuum pump overnight and is hydrated the following day with deionized water. The sample is then sonicated for 2 hours in a capped vial, using a Heat Systems model 350 sonicator equipped with an inverted cup (bath type) probe at the maximum setting while the bath is circulated at 15EC. Alternatively, negatively charged vesicles can be prepared without sonication to produce multilamellar vesicles or by extrusion through nucleopore membranes to produce unilamellar vesicles of discrete size. Other methods are known and available to those of skill in the art.

[0364] The liposomes can comprise multilamellar vesicles (MLVs), small unilamellar vesicles (SUVs), or large unilamellar vesicles (LUVs), with SUVs being preferred. The various liposome-nucleic acid complexes are prepared using methods well known in the art. See, e.g., Straubinger et al., Methods of Immunology (1983), 101:512-527, which is herein incorporated by reference. For example, MLVs containing nucleic acid can be prepared by depositing a thin film of phospholipid on the walls of a glass tube and subsequently hydrating with a solution of the material to be encapsulated. SUVs are prepared by extended sonication of MLVs to produce a homogeneous population of unilamellar liposomes. The material to be entrapped is added to a suspension of preformed MLVs and then sonicated. When using liposomes containing cationic lipids, the dried lipid film is resuspended in an appropriate solution such as sterile

water or an isotonic buffer solution such as 10 mM Tris/NaCl, sonicated, and then the preformed liposomes are mixed directly with the DNA. The liposome and DNA form a very stable complex due to binding of the positively charged liposomes to the cationic DNA. SUVs find use with small nucleic acid fragments. LUVs are prepared by a number of methods, well known in the art. Commonly used methods include Ca^{2+}-EDTA chelation (Papahadjopoulos et al., Biochim. Biophys. Acta (1975) 394:483; Wilson et al., Cell (1979) 17:77); ether injection (Deamer, D. and Bangham, A., Biochim. Biophys. Acta (1976) 443:629; Ostro et al., Biochem. Biophys. Res. Commun. (1977) 76:836; Fraley et al., Proc. Natl. Acad. Sci. USA (1979) 76:3348); detergent dialysis (Enoch, H. and Strittmatter, P., Proc. Natl. Acad. Sci. USA (1979) 76:145); and reverse-phase evaporation (REV) (Fraley et al., J. Biol. Chem. (1980) 255:10431; Szoka, F. and Papahadjopoulos, D., Proc. Natl. Acad. Sci. USA (1978) 75:145; Schaefer-Ridder et al., Science (1982) 215:166), which are herein incorporated by reference.

[0365] Generally, the ratio of DNA to liposomes will be from about 10:1 to about 1:10. Preferably, the ration will be from about 5:1 to about 1:5. More preferably, the ration will be about 3:1 to about 1:3. Still more preferably, the ratio will be about 1:1.

[0366] U.S. Patent No. 5,676,954 (which is herein incorporated by reference) reports on the injection of genetic material, complexed with cationic liposomes carriers, into mice. U.S. Patent Nos. 4,897,355, 4,946,787, 5,049,386, 5,459,127, 5,589,466, 5,693,622, 5,580,859, 5,703,055, and international publication no. WO 94/9469 (which are herein incorporated by reference) provide cationic lipids for use in transfecting DNA into cells and mammals. U.S. Patent Nos. 5,589,466, 5,693,622, 5,580,859, 5,703,055, and international publication no. WO 94/9469 (which are herein incorporated by reference) provide methods for delivering DNA-cationic lipid complexes to mammals.

[0367] In certain embodiments, cells are engineered, ex vivo or in vivo, using a retroviral particle containing RNA which comprises a sequence encoding a polypeptide of the present invention. Retroviruses from which the retroviral plasmid vectors may be derived include, but are not limited to, Moloney Murine Leukemia Virus, spleen necrosis virus, Rous sarcoma Virus, Harvey Sarcoma Virus, avian leukosis virus, gibbon ape leukemia virus, human immunodeficiency virus, Myeloproliferative Sarcoma Virus, and mammary tumor virus.

[0368] The retroviral plasmid vector is employed to transduce packaging cell lines to form producer cell lines. Examples of packaging cells which may be transfected include, but are not limited to, the PE501, PA317, R-2, R-AM, PA12, T19-14X, VT-19-17-H2, RCRE, RCRIP, GP+E-86, GP+envAm12, and DAN cell lines as described in Miller, Human Gene Therapy 1:5-14 (1990), which is incorporated herein by reference in its entirety. The vector may transduce the packaging cells through any means known in the art. Such means include, but are not limited to, electroporation, the use of liposomes, and $CaPO_4$ precipitation. In one alternative, the retroviral plasmid vector may be encapsulated into a liposome, or coupled to a lipid, and then administered to a host.

[0369] The producer cell line generates infectious retroviral vector particles which include polynucleotide encoding a polypeptide of the present invention. Such retroviral vector particles then may be employed, to transduce eukaryotic cells, either in vitro or in vivo. The transduced eukaryotic cells will express a polypeptide of the present invention.

[0370] In certain other embodiments, cells are engineered, ex vivo or in vivo, with polynucleotide contained in an adenovirus vector. Adenovirus can be manipulated such that it encodes and expresses a polypeptide of the present invention, and at the same time is inactivated in terms of its ability to replicate in a normal lytic viral life cycle. Adenovirus expression is achieved without integration of the viral DNA into the host cell chromosome, thereby alleviating concerns about insertional mutagenesis. Furthermore, adenoviruses have been used as live enteric vaccines for many years with an excellent safety profile (Schwartz, A. R. et al. (1974) Am. Rev. Respir. Dis.109:233-238). Finally, adenovirus mediated gene transfer has been demonstrated in a number of instances including transfer of alpha-1-antitrypsin and CFTR to the lungs of cotton rats (Rosenfeld, M. A. et al. (1991) Science 252:431-434; Rosenfeld et al., (1992) Cell 68:143-155). Furthermore, extensive studies to attempt to establish adenovirus as a causative agent in human cancer were uniformly negative (Green, M. et al. (1979) Proc. Natl. Acad. Sci. USA 76:6606).

[0371] Suitable adenoviral vectors useful in the present invention are described, for example, in Kozarsky and Wilson, Curr. Opin. Genet. Devel. 3:499-503 (1993); Rosenfeld et al., Cell 68:143-155 (1992); Engelhardt et al., Human Genet. Ther. 4:759-769 (1993); Yang et al., Nature Genet. 7:362-369 (1994); Wilson et al., Nature 365:691-692 (1993); and U.S. Patent No. 5,652,224, which are herein incorporated by reference.

For example, the adenovirus vector Ad2 is useful and can be grown in human 293 cells. These cells contain the El region of adenovirus and constitutively express Ela and Elb, which complement the defective adenoviruses by providing the products of the genes deleted from the vector. In addition to Ad2, other varieties of adenovirus (e.g., Ad3, Ad5, and Ad7) are also useful in the present invention.

[0372] Preferably, the adenoviruses used in the present invention are replication deficient. Replication deficient adenoviruses require the aid of a helper virus and/or packaging cell line to form infectious particles. The resulting virus is capable of infecting cells and can express a polynucleotide of interest which is operably linked to a promoter, but cannot replicate in most cells. Replication deficient adenoviruses may be deleted in one or more of all or a portion of the following genes: Ela, Elb, E3, E4, E2a, or L1 through L5.

[0373] In certain other embodiments, the cells are engineered, ex vivo or in vivo, using an adeno-associated virus (AAV). AAVs are naturally occurring defective viruses that require helper viruses to produce infectious particles (Muzyczka, N., Curr. Topics in Microbiol. Immunol. 158:97 (1992)). It is also one of the few viruses that may integrate its DNA into non-dividing cells. Vectors containing as little as 300 base pairs of AAV can be packaged and can integrate, but space for exogenous DNA is limited to about 4.5 kb. Methods for producing and using such AAVs are known in the art. See, for example, U.S. Patent Nos. 5,139,941, 5,173,414, 5,354,678, 5,436,146, 5,474,935, 5,478,745, and 5,589,377.

[0374] For example, an appropriate AAV vector for use in the present invention will include all the sequences necessary for DNA replication, encapsidation, and host-cell integration. The polynucleotide construct is inserted into the AAV vector using standard cloning methods, such as those found in Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press (1989). The recombinant AAV vector is then transfected into packaging cells which are infected with a helper virus, using any standard technique, including lipofection, electroporation, calcium phosphate precipitation, etc. Appropriate helper viruses include adenoviruses, cytomegaloviruses, vaccinia viruses, or herpes viruses. Once the packaging cells are transfected and infected, they will produce infectious AAV viral particles which contain the polynucleotide construct. These viral particles are then used to transduce eukaryotic cells, either ex vivo

or in vivo. The transduced cells will contain the polynucleotide construct integrated into its genome, and will express a polypeptide of the invention.

[0375] Another method of gene therapy involves operably associating heterologous control regions and endogenous polynucleotide sequences (e.g. encoding a polypeptide of the present invention) via homologous recombination (see, e.g., U.S. Patent No. 5,641,670, issued June 24, 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989). This method involves the activation of a gene which is present in the target cells, but which is not normally expressed in the cells, or is expressed at a lower level than desired.

[0376] Polynucleotide constructs are made, using standard techniques known in the art, which contain the promoter with targeting sequences flanking the promoter. Suitable promoters are described herein. The targeting sequence is sufficiently complementary to an endogenous sequence to permit homologous recombination of the promoter-targeting sequence with the endogenous sequence. The targeting sequence will be sufficiently near the 5' end of the desired endogenous polynucleotide sequence so the promoter will be operably linked to the endogenous sequence upon homologous recombination.

[0377] The promoter and the targeting sequences can be amplified using PCR. Preferably, the amplified promoter contains distinct restriction enzyme sites on the 5' and 3' ends. Preferably, the 3' end of the first targeting sequence contains the same restriction enzyme site as the 5' end of the amplified promoter and the 5' end of the second targeting sequence contains the same restriction site as the 3' end of the amplified promoter. The amplified promoter and targeting sequences are digested and ligated together.

[0378] The promoter-targeting sequence construct is delivered to the cells, either as naked polynucleotide, or in conjunction with transfection-facilitating agents, such as liposomes, viral sequences, viral particles, whole viruses, lipofection, precipitating agents, etc., described in more detail above. The P promoter-targeting sequence can be delivered by any method, included direct needle injection, intravenous injection, topical administration, catheter infusion, particle accelerators, etc. The methods are described in more detail below.

[0379] The promoter-targeting sequence construct is taken up by cells. Homologous recombination between the construct and the endogenous sequence takes place, such that an endogenous sequence is placed under the control of the promoter. The promoter then drives the expression of the endogenous sequence.

[0380] Preferably, the polynucleotide encoding a polypeptide of the present invention contains a secretory signal sequence that facilitates secretion of the protein. Typically, the signal sequence is positioned in the coding region of the polynucleotide to be expressed towards or at the 5' end of the coding region. The signal sequence may be homologous or heterologous to the polynucleotide of interest and may be homologous or heterologous to the cells to be transfected. Additionally, the signal sequence may be chemically synthesized using methods known in the art.

[0381] Any mode of administration of any of the above-described polynucleotides constructs can be used so long as the mode results in the expression of one or more molecules in an amount sufficient to provide a therapeutic effect. This includes direct needle injection, systemic injection, catheter infusion, biolistic injectors, particle accelerators (i.e., "gene guns"), gelfoam sponge depots, other commercially available depot materials, osmotic pumps (e.g., Alza minipumps), oral or suppositorial solid (tablet or pill) pharmaceutical formulations, and decanting or topical applications during surgery. For example, direct injection of naked calcium phosphate-precipitated plasmid into rat liver and rat spleen or a protein-coated plasmid into the portal vein has resulted in gene expression of the foreign gene in the rat livers (Kaneda et al., Science 243:375 (1989)).

[0382] A preferred method of local administration is by direct injection. Preferably, a recombinant molecule of the present invention complexed with a delivery vehicle is administered by direct injection into or locally within the area of arteries. Administration of a composition locally within the area of arteries refers to injecting the composition centimeters and preferably, millimeters within arteries.

[0383] Another method of local administration is to contact a polynucleotide construct of the present invention in or around a surgical wound. For example, a patient can undergo surgery and the polynucleotide construct can be coated on the surface of tissue inside the wound or the construct can be injected into areas of tissue inside the wound.

[0384] Therapeutic compositions useful in systemic administration, include recombinant molecules of the present invention complexed to a targeted delivery vehicle of the present invention. Suitable delivery vehicles for use with systemic administration comprise liposomes comprising ligands for targeting the vehicle to a particular site.

[0385] Preferred methods of systemic administration, include intravenous injection, aerosol, oral and percutaneous (topical) delivery. Intravenous injections can be performed using methods standard in the art. Aerosol delivery can also be performed using methods standard in the art (see, for example, Stribling et al., Proc. Natl. Acad. Sci. USA 189:11277-11281, 1992, which is incorporated herein by reference). Oral delivery can be performed by complexing a polynucleotide construct of the present invention to a carrier capable of withstanding degradation by digestive enzymes in the gut of an animal. Examples of such carriers, include plastic capsules or tablets, such as those known in the art. Topical delivery can be performed by mixing a polynucleotide construct of the present invention with a lipophilic reagent (e.g., DMSO) that is capable of passing into the skin.

[0386] Determining an effective amount of substance to be delivered can depend upon a number of factors including, for example, the chemical structure and biological activity of the substance, the age and weight of the animal, the precise condition requiring treatment and its severity, and the route of administration. The frequency of treatments depends upon a number of factors, such as the amount of polynucleotide constructs administered per dose, as well as the health and history of the subject. The precise amount, number of doses, and timing of doses will be determined by the attending physician or veterinarian.

[0387] Therapeutic compositions of the present invention can be administered to any animal, preferably to mammals and birds. Preferred mammals include humans, dogs, cats, mice, rats, rabbits sheep, cattle, horses and pigs, with humans being particularly preferred.

Biological Activities

[0388] Polynucleotides or polypeptides, or agonists or antagonists of the present invention, can be used in assays to test for one or more biological activities. If these polynucleotides or polypeptides, or agonists or antagonists of the present invention, do exhibit activity in a particular assay, it is likely that these molecules may be involved in

the diseases associated with the biological activity. Thus, the polynucleotides and polypeptides, and agonists or antagonists could be used to treat, prevent diagnose and/or prognose the associated disease.

[0389] The prostate cancer antigen polynucleotides and polypeptides of the invention are predicted to have predominant expression in prostate tissues.

[0390] Thus, the prostate cancer antigens of the invention (e.g., polynucleotides of the invention (e.g., nucleotide coding sequence in SEQ ID NO:X, the nucleotide coding sequence of the related cDNA contained in a deposited library or fragments or variants thereof), polypeptides of the invention (e.g., the polypeptide of SEQ ID NO:Y, a polypeptide encoded by SEQ ID NO:X, a polypeptide encoded by the cDNA in the related cDNA clone contained in a deposited library, and/or fragments or variants thereof), and/or an antibody, or fragment thereof, directed to a polypeptide of the invention) may be useful as therapeutic molecules. Each would be useful for diagnosis, detection, treatment and/or prevention of diseases or disorders of the prostate, including but not limited to prostate cancers such as adenocarcinoma, transitional cell carcinomas, ductal carcinomas, and squamous cell carcinomas.

[0391] Particularly, the prostate cancer antigens may be a useful therapeutic for prostate cancer. Treatment, diagnosis, detection, and/or prevention of prostate disorders could be carried out using a prostate cancer antigen or soluble form of a prostate cancer antigen, a prostate cancer antigen ligand, gene therapy, or ex vivo applications. Moreover, inhibitors of a prostate cancer antigen, either blocking antibodies or mutant forms, could modulate the expression of the prostate cancer antigen. These inhibitors may be useful to treat, diagnose, detect, and/or prevent diseases associated with the misregulation of a prostate cancer antigen.

[0392] In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells (e.g., normal or diseased prostate cells) by administering polypeptides of the invention (e.g., prostate cancer antigen polypeptides or anti- prostate cancer antigen antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a therapeutic protein into the targeted cell (e.g., an aberrant prostate cell or prostate cancer cell). In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid

(e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

[0393] In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of aberrant prostate cells, including, but not limited to, prostate tumor cells) by administering polypeptides of the invention (e.g., prostate cancer antigen polypeptides or fragments thereof, or anti- prostate cancer antigen antibodies) in association with toxins or cytotoxic prodrugs.

[0394] By "toxin" is meant compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, cytotoxins (cytotoxic agents), or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNAse, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. "Toxin" also includes a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, ^{213}Bi, or other radioisotopes such as, for example, ^{103}Pd, ^{133}Xe, ^{131}I, ^{68}Ge, ^{57}Co, ^{65}Zn, ^{85}Sr, ^{32}P, ^{35}S, ^{90}Y, ^{153}Sm, ^{153}Gd, ^{169}Yb, ^{51}Cr, ^{54}Mn, ^{75}Se, ^{113}Sn, ^{90}Yttrium, ^{117}Tin, ^{186}Rhenium, ^{166}Holmium, and ^{188}Rhenium; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

[0395] Techniques known in the art may be applied to label antibodies of the invention. Such techniques include, but are not limited to, the use of bifunctional conjugating agents (see e.g., U.S. Patent Nos. 5,756,065; 5,714,631; 5,696,239; 5,652,361; 5,505,931; 5,489,425; 5,435,990; 5,428,139; 5,342,604; 5,274,119; 4,994,560; and 5,808,003; the contents of each of which are hereby incorporated by reference in its entirety). A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and

puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclothosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis- dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine).

[0396] By "cytotoxic prodrug" is meant a non-toxic compound that is converted by an enzyme, normally present in the cell, into a cytotoxic compound. Cytotoxic prodrugs that may be used according to the methods of the invention include, but are not limited to, glutamyl derivatives of benzoic acid mustard alkylating agent, phosphate derivatives of etoposide or mitomycin C, cytosine arabinoside, daunorubisin, and phenoxyacetamide derivatives of doxorubicin.

[0397] It will be appreciated that conditions caused by a decrease in the standard or normal level of a prostate cancer antigen activity in an individual, particularly disorders of the prostate, can be treated by administration of a prostate cancer antigen polypeptide (e.g., such as, for example, the complete prostate cancer antigen polypeptide, the soluble form of the extracellular domain of a prostate cancer antigen polypeptide, or cells expressing the complete protein) or agonist. Thus, the invention also provides a method of treatment of an individual in need of an increased level of prostate cancer antigen activity comprising administering to such an individual a pharmaceutical composition comprising an amount of an isolated prostate cancer antigen polypeptide of the invention, or agonist thereof (e.g., an agonistic anti- prostate cancer antigen antibody), effective to increase the prostate cancer antigen activity level in such an individual.

[0398] It will also be appreciated that conditions caused by a increase in the standard or normal level of prostate cancer antigen activity in an individual, particularly disorders of the prostate, can be treated by administration of prostate cancer antigen polypeptides (e.g., such as, for example, the complete prostate cancer antigen polypeptide, the soluble form of the extracellular domain of a prostate cancer antigen polypeptide, or cells expressing the complete protein) or antagonist (e.g., an antagonistic prostate cancer

antigen antibody). Thus, the invention also provides a method of treatment of an individual in need of an decreased level of prostate cancer antigen activity comprising administering to such an individual a pharmaceutical composition comprising an amount of an isolated prostate cancer antigen polypeptide of the invention, or antagonist thereof (e.g., an antagonistic anti-prostate cancer antigen antibody), effective to decrease the prostate cancer antigen activity level in such an individual.

[0399] More generally, polynucleotides, translation products and antibodies corresponding to this gene may be useful for the diagnosis, prognosis, prevention, and/or treatment of diseases and/or disorders associated with the following systems.

Reproductive System Disorders

[0400] The polynucleotides or polypeptides, or agonists or antagonists of the invention may be used for the diagnosis, treatment, or prevention of diseases and/or disorders of the reproductive system. Reproductive system disorders that can be treated by the compositions of the invention, include, but are not limited to, reproductive system injuries, infections, neoplastic disorders, congenital defects, and diseases or disorders which result in infertility, complications with pregnancy, labor, or parturition, and postpartum difficulties.

[0401] Reproductive system disorders and/or diseases include diseases and/or disorders of the testes, including, but not limited to, testicular atrophy, testicular feminization, cryptorchism (unilateral and bilateral), anorchia, ectopic testis, epididymitis and orchitis (typically resulting from infections such as, for example, gonorrhea, mumps, tuberculosis, and syphilis), testicular torsion, vasitis nodosa, germ cell tumors (e.g., seminomas, embryonal cell carcinomas, teratocarcinomas, choriocarcinomas, yolk sac tumors, and teratomas), stromal tumors (e.g., Leydig cell tumors), hydrocele, hematocele, varicocele, spermatocele, inguinal hernia, and disorders of sperm production (e.g., immotile cilia syndrome, aspermia, asthenozoospermia, azoospermia, oligospermia, and teratozoospermia).

[0402] Reproductive system disorders also include, but are not limited to, disorders of the prostate gland, such as acute non-bacterial prostatitis, chronic non-bacterial prostatitis, acute bacterial prostatitis, chronic bacterial prostatitis, prostatodystonia, prostatosis, granulomatous prostatitis, malacoplakia, benign prostatic

hypertrophy or hyperplasia, and prostate neoplastic disorders, including adenocarcinomas, transitional cell carcinomas, ductal carcinomas, and squamous cell carcinomas.

[0403] Additionally, the compositions of the invention may be useful in the diagnosis, treatment, and/or prevention of disorders or diseases of the penis and urethra, including, but not limited to, inflammatory disorders, such as balanoposthitis, balanitis xerotica obliterans, phimosis, paraphimosis, syphilis, herpes simplex virus, gonorrhea, non-gonococcal urethritis, chlamydia, mycoplasma, trichomonas, HIV, AIDS, Reiter's syndrome, condyloma acuminatum, condyloma latum, and pearly penile papules; urethral abnormalities, such as hypospadias, epispadias, and phimosis; premalignant lesions, including Erythroplasia of Queyrat, Bowen's disease, Bowenoid paplosis, giant condyloma of Buscke-Lowenstein, and varrucous carcinoma; penile cancers, including squamous cell carcinomas, carcinoma in situ, verrucous carcinoma, and disseminated penile carcinoma; urethral neoplastic disorders, including penile urethral carcinoma, bulbomembranous urethral carcinoma, and prostatic urethral carcinoma; and erectile disorders, such as priapism, Peyronie's disease, erectile dysfunction, and impotence.

[0404] Moreover, diseases and/or disorders of the vas deferens include, but are not limited to, vasculititis and CBAVD (congenital bilateral absence of the vas deferens); additionally, the polynucleotides, polypeptides, and agonists or antagonists of the present invention may be used in the diagnosis, treatment, and/or prevention of diseases and/or disorders of the seminal vesicles, including but not limited to, hydatid disease, congenital chloride diarrhea, and polycystic kidney disease.

[0405] Other disorders and/or diseases of the male reproductive system that may be diagnosed, treated, and/or prevented with the compositions of the invention include, but are not limited to, Klinefelter's syndrome, Young's syndrome, premature ejaculation, diabetes mellitus, cystic fibrosis, Kartagener's syndrome, high fever, multiple sclerosis, and gynecomastia.

[0406] Further, the polynucleotides, polypeptides, and agonists or antagonists of the present invention may be used in the diagnosis, treatment, and/or prevention of diseases and/or disorders of the vagina and vulva, including, but not limited to, bacterial vaginosis, candida vaginitis, herpes simplex virus, chancroid, granuloma inguinale, lymphogranuloma venereum, scabies, human papillomavirus, vaginal trauma, vulvar trauma, adenosis, chlamydia vaginitis, gonorrhea, trichomonas vaginitis, condyloma

acuminatum, syphilis, molluscum contagiosum, atrophic vaginitis, Paget's disease, lichen sclerosus, lichen planus, vulvodynia, toxic shock syndrome, vaginismus, vulvovaginitis, vulvar vestibulitis, and neoplastic disorders, such as squamous cell hyperplasia, clear cell carcinoma, basal cell carcinoma, melanomas, cancer of Bartholin's gland, and vulvar intraepithelial neoplasia.

[0407] Disorders and/or diseases of the uterus that may be diagnosed, treated, and/or prevented with the compositions of the invention include, but are not limited to, dysmenorrhea, retroverted uterus, endometriosis, fibroids, adenomyosis, anovulatory bleeding, amenorrhea, Cushing's syndrome, hydatidiform moles, Asherman's syndrome, premature menopause, precocious puberty, uterine polyps, dysfunctional uterine bleeding (e.g., due to aberrant hormonal signals), and neoplastic disorders, such as adenocarcinomas, keiomyosarcomas, and sarcomas. Additionally, the polypeptides, polynucleotides, or agonists or antagonists of the invention may be useful as a marker or detector of, as well as in the diagnosis, treatment, and/or prevention of congenital uterine abnormalities, such as bicornuate uterus, septate uterus, simple unicornuate uterus, unicornuate uterus with a noncavitary rudimentary horn, unicornuate uterus with a non-communicating cavitary rudimentary horn, unicornuate uterus with a communicating cavitary horn, arcuate uterus, uterine didelfus, and T-shaped uterus.

[0408] Ovarian diseases and/or disorders that may be diagnosed, treated, and/or prevented with the compositions of the invention include, but are not limited to, anovulation, polycystic ovary syndrome (Stein-Leventhal syndrome), ovarian cysts, ovarian hypofunction, ovarian insensitivity to gonadotropins, ovarian overproduction of androgens, right ovarian vein syndrome, amenorrhea, hirutism, and ovarian cancer (including, but not limited to, primary and secondary cancerous growth, Sertoli-Leydig tumors, endometriod carcinoma of the ovary, ovarian papillary serous adenocarcinoma, ovarian mucinous adenocarcinoma, and Ovarian Krukenberg tumors).

[0409] Cervical diseases and/or disorders that may be diagnosed, treated, and/or prevented with the compositions of the invention include, but are not limited to, cervicitis, chronic cervicitis, mucopurulent cervicitis, cervical dysplasia, cervical polyps, Nabothian cysts, cervical erosion, cervical incompetence, and cervical neoplasms (including, for example, cervical carcinoma, squamous metaplasia, squamous cell carcinoma, adenosquamous cell neoplasia, and columnar cell neoplasia).

[0410] Additionally, diseases and/or disorders of the reproductive system that may be diagnosed, treated, and/or prevented with the compositions of the invention include, but are not limited to, disorders and/or diseases of pregnancy, including miscarriage and stillbirth, such as early abortion, late abortion, spontaneous abortion, induced abortion, therapeutic abortion, threatened abortion, missed abortion, incomplete abortion, complete abortion, habitual abortion, missed abortion, and septic abortion; ectopic pregnancy, anemia, Rh incompatibility, vaginal bleeding during pregnancy, gestational diabetes, intrauterine growth retardation, polyhydramnios, HELLP syndrome, abruptio placentae, placenta previa, hyperemesis, preeclampsia, eclampsia, herpes gestationis, and urticaria of pregnancy. Additionally, the polynucleotides, polypeptides, and agonists or antagonists of the present invention may be used in the diagnosis, treatment, and/or prevention of diseases that can complicate pregnancy, including heart disease, heart failure, rheumatic heart disease, congenital heart disease, mitral valve prolapse, high blood pressure, anemia, kidney disease, infectious disease (e.g., rubella, cytomegalovirus, toxoplasmosis, infectious hepatitis, chlamydia, HIV, AIDS, and genital herpes), diabetes mellitus, Graves' disease, thyroiditis, hypothyroidism, Hashimoto's thyroiditis, chronic active hepatitis, cirrhosis of the liver, primary biliary cirrhosis, asthma, systemic lupus eryematosis, rheumatoid arthritis, myasthenia gravis, idiopathic thrombocytopenic purpura, appendicitis, ovarian cysts, gallbladder disorders,and obstruction of the intestine.

[0411] Complications associated with labor and parturition that may be diagnosed, treated, and/or prevented with the compositions of the invention include, but are not limited to, premature rupture of the membranes, pre-term labor, post-term pregnancy, postmaturity, labor that progresses too slowly, fetal distress (e.g., abnormal heart rate (fetal or maternal), breathing problems, and abnormal fetal position), shoulder dystocia, prolapsed umbilical cord, amniotic fluid embolism, and aberrant uterine bleeding.

[0412] Further, diseases and/or disorders of the postdelivery period, that may be diagnosed, treated, and/or prevented with the compositions of the invention, include, but are not limited to, endometritis, myometritis, parametritis, peritonitis, pelvic thrombophlebitis, pulmonary embolism, endotoxemia, pyelonephritis, saphenous thrombophlebitis, mastitis, cystitis, postpartum hemorrhage, and inverted uterus.

[0413] Other disorders and/or diseases of the female reproductive system that may be diagnosed, treated, and/or prevented by the polynucleotides, polypeptides, and agonists

or antagonists of the present invention include, but are not limited to, Turner's syndrome, pseudohermaphroditism, premenstrual syndrome, pelvic inflammatory disease, pelvic congestion (vascular engorgement), frigidity, anorgasmia, dyspareunia, ruptured fallopian tube, and Mittelschmerz.

Immune Activity

[0414] Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, diagnosing and/or prognosing diseases, disorders, and/or conditions of the immune system, by, for example, activating or inhibiting the proliferation, differentiation, or mobilization (chemotaxis) of immune cells. Immune cells develop through a process called hematopoiesis, producing myeloid (platelets, red blood cells, neutrophils, and macrophages) and lymphoid (B and T lymphocytes) cells from pluripotent stem cells. The etiology of these immune diseases, disorders, and/or conditions may be genetic, somatic, such as cancer and some autoimmune diseases, acquired (e.g., by chemotherapy or toxins), or infectious. Moreover, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention can be used as a marker or detector of a particular immune system disease or disorder.

[0415] Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, diagnosing, and/or prognosing immunodeficiencies, including both congenital and acquired immunodeficiencies. Examples of B cell immunodeficiencies in which immunoglobulin levels B cell function and/or B cell numbers are decreased include: X-linked agammaglobulinemia (Bruton's disease), X-linked infantile agammaglobulinemia, X-linked immunodeficiency with hyper IgM, non X-linked immunodeficiency with hyper IgM, X-linked lymphoproliferative syndrome (XLP), agammaglobulinemia including congenital and acquired agammaglobulinemia, adult onset agammaglobulinemia, late-onset agammaglobulinemia, dysgammaglobulinemia, hypogammaglobulinemia, unspecified hypogammaglobulinemia, recessive agammaglobulinemia (Swiss type), Selective IgM deficiency, selective IgA deficiency, selective IgG subclass deficiencies, IgG subclass deficiency (with or without IgA deficiency), Ig deficiency with increased IgM, IgG and IgA deficiency with increased IgM, antibody deficiency with normal or elevated Igs, Ig heavy chain deletions, kappa

chain deficiency, B cell lymphoproliferative disorder (BLPD), common variable immunodeficiency (CVID), common variable immunodeficiency (CVI) (acquired), and transient hypogammaglobulinemia of infancy.

[0416] In specific embodiments, ataxia-telangiectasia or conditions associated with ataxia-telangiectasia are treated, prevented, diagnosed, and/or prognosing using the polypeptides or polynucleotides of the invention, and/or agonists or antagonists thereof.

[0417] Examples of congenital immunodeficiencies in which T cell and/or B cell function and/or number is decreased include, but are not limited to: DiGeorge anomaly, severe combined immunodeficiencies (SCID) (including, but not limited to, X-linked SCID, autosomal recessive SCID, adenosine deaminase deficiency, purine nucleoside phosphorylase (PNP) deficiency, Class II MHC deficiency (Bare lymphocyte syndrome), Wiskott-Aldrich syndrome, and ataxia telangiectasia), thymic hypoplasia, third and fourth pharyngeal pouch syndrome, 22q11.2 deletion, chronic mucocutaneous candidiasis, natural killer cell deficiency (NK), idiopathic CD4+ T-lymphocytopenia, immunodeficiency with predominant T cell defect (unspecified), and unspecified immunodeficiency of cell mediated immunity.

[0418] In specific embodiments, DiGeorge anomaly or conditions associated with DiGeorge anomaly are treated, prevented, diagnosed, and/or prognosed using polypeptides or polynucleotides of the invention, or antagonists or agonists thereof.

[0419] Other immunodeficiencies that may be treated, prevented, diagnosed, and/or prognosed using polypeptides or polynucleotides of the invention, and/or agonists or antagonists thereof, include, but are not limited to, chronic granulomatous disease, Chédiak-Higashi syndrome, myeloperoxidase deficiency, leukocyte glucose-6-phosphate dehydrogenase deficiency, X-linked lymphoproliferative syndrome (XLP), leukocyte adhesion deficiency, complement component deficiencies (including C1, C2, C3, C4, C5, C6, C7, C8 and/or C9 deficiencies), reticular dysgenesis, thymic alymphoplasia-aplasia, immunodeficiency with thymoma, severe congenital leukopenia, dysplasia with immunodeficiency, neonatal neutropenia, short limbed dwarfism, and Nezelof syndrome-combined immunodeficiency with Igs.

[0420] In a preferred embodiment, the immunodeficiencies and/or conditions associated with the immunodeficiencies recited above are treated, prevented, diagnosed

and/or prognosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.

[0421] In a preferred embodiment polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention could be used as an agent to boost immunoresponsiveness among immunodeficient individuals. In specific embodiments, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention could be used as an agent to boost immunoresponsiveness among B cell and/or T cell immunodeficient individuals.

[0422] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, diagnosing and/or prognosing autoimmune disorders. Many autoimmune disorders result from inappropriate recognition of self as foreign material by immune cells. This inappropriate recognition results in an immune response leading to the destruction of the host tissue. Therefore, the administration of polynucleotides and polypeptides of the invention that can inhibit an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing autoimmune disorders.

[0423] Autoimmune diseases or disorders that may be treated, prevented, diagnosed and/or prognosed by polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention include, but are not limited to, one or more of the following: systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, multiple sclerosis, autoimmune thyroiditis, Hashimoto's thyroiditis, autoimmune hemolytic anemia, hemolytic anemia, thrombocytopenia, autoimmune thrombocytopenia purpura, autoimmune neonatal thrombocytopenia, idiopathic thrombocytopenia purpura, purpura (e.g., Henloch-Scoenlein purpura), autoimmunocytopenia, Goodpasture's syndrome, Pemphigus vulgaris, myasthenia gravis, Grave's disease (hyperthyroidism), and insulin-resistant diabetes mellitus.

[0424] Additional disorders that are likely to have an autoimmune component that may be treated, prevented, and/or diagnosed with the compositions of the invention include, but are not limited to, type II collagen-induced arthritis, antiphospholipid syndrome, dermatitis, allergic encephalomyelitis, myocarditis, relapsing polychondritis, rheumatic heart disease, neuritis, uveitis ophthalmia, polyendocrinopathies, Reiter's Disease, Stiff-Man Syndrome, autoimmune pulmonary inflammation, autism, Guillain-

Barre Syndrome, insulin dependent diabetes mellitus, and autoimmune inflammatory eye disorders.

[0425] Additional disorders that are likely to have an autoimmune component that may be treated, prevented, diagnosed and/or prognosed with the compositions of the invention include, but are not limited to, scleroderma with anti-collagen antibodies (often characterized, e.g., by nucleolar and other nuclear antibodies), mixed connective tissue disease (often characterized, e.g., by antibodies to extractable nuclear antigens (e.g., ribonucleoprotein)), polymyositis (often characterized, e.g., by nonhistone ANA), pernicious anemia (often characterized, e.g., by antiparietal cell, microsomes, and intrinsic factor antibodies), idiopathic Addison's disease (often characterized, e.g., by humoral and cell-mediated adrenal cytotoxicity, infertility (often characterized, e.g., by antispermatozoal antibodies), glomerulonephritis (often characterized, e.g., by glomerular basement membrane antibodies or immune complexes), bullous pemphigoid (often characterized, e.g., by IgG and complement in basement membrane), Sjogren's syndrome (often characterized, e.g., by multiple tissue antibodies, and/or a specific nonhistone ANA (SS-B)), diabetes mellitus (often characterized, e.g., by cell-mediated and humoral islet cell antibodies), and adrenergic drug resistance (including adrenergic drug resistance with asthma or cystic fibrosis) (often characterized, e.g., by beta-adrenergic receptor antibodies).

[0426] Additional disorders that may have an autoimmune component that may be treated, prevented, diagnosed and/or prognosed with the compositions of the invention include, but are not limited to, chronic active hepatitis (often characterized, e.g., by smooth muscle antibodies), primary biliary cirrhosis (often characterized, e.g., by mitochondria antibodies), other endocrine gland failure (often characterized, e.g., by specific tissue antibodies in some cases), vitiligo (often characterized, e.g., by melanocyte antibodies), vasculitis (often characterized, e.g., by Ig and complement in vessel walls and/or low serum complement), post-MI (often characterized, e.g., by myocardial antibodies), cardiotomy syndrome (often characterized, e.g., by myocardial antibodies), urticaria (often characterized, e.g., by IgG and IgM antibodies to IgE), atopic dermatitis (often characterized, e.g., by IgG and IgM antibodies to IgE), asthma (often characterized, e.g., by IgG and IgM antibodies to IgE), and many other inflammatory, granulomatous, degenerative, and atrophic disorders.

[0427] In a preferred embodiment, the autoimmune diseases and disorders and/or conditions associated with the diseases and disorders recited above are treated, prevented, diagnosed and/or prognosed using for example, antagonists or agonists, polypeptides or polynucleotides, or antibodies of the present invention. In a specific preferred embodiment, rheumatoid arthritis is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.

[0428] In another specific preferred embodiment, systemic lupus erythematosus is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention. In another specific preferred embodiment, idiopathic thrombocytopenia purpura is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.

[0429] In another specific preferred embodiment IgA nephropathy is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.

[0430] In a preferred embodiment, the autoimmune diseases and disorders and/or conditions associated with the diseases and disorders recited above are treated, prevented, diagnosed and/or prognosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention.

[0431] In preferred embodiments, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a immunosuppressive agent(s).

[0432] Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, prognosing, and/or diagnosing diseases, disorders, and/or conditions of hematopoietic cells. Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat or prevent those diseases, disorders, and/or conditions associated with a decrease in certain (or many) types hematopoietic cells, including but not limited to, leukopenia, neutropenia, anemia, and thrombocytopenia. Alternatively, Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention could be used to increase differentiation and proliferation of

hematopoietic cells, including the pluripotent stem cells, in an effort to treat or prevent those diseases, disorders, and/or conditions associated with an increase in certain (or many) types of hematopoietic cells, including but not limited to, histiocytosis.

[0433] Allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems, may also be treated, prevented, diagnosed and/or prognosed using polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof. Moreover, these molecules can be used to treat, prevent, prognose, and/or diagnose anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.

[0434] Additionally, polypeptides or polynucleotides of the invention, and/or agonists or antagonists thereof, may be used to treat, prevent, diagnose and/or prognose IgE-mediated allergic reactions. Such allergic reactions include, but are not limited to, asthma, rhinitis, and eczema. In specific embodiments, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to modulate IgE concentrations in vitro or in vivo.

[0435] Moreover, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention have uses in the diagnosis, prognosis, prevention, and/or treatment of inflammatory conditions. For example, since polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists of the invention may inhibit the activation, proliferation and/or differentiation of cells involved in an inflammatory response, these molecules can be used to prevent and/or treat chronic and acute inflammatory conditions. Such inflammatory conditions include, but are not limited to, for example, inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome), ischemia-reperfusion injury, endotoxin lethality, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, over production of cytokines (e.g., TNF or IL-1.), respiratory disorders (e.g., asthma and allergy); gastrointestinal disorders (e.g., inflammatory bowel disease); cancers (e.g., gastric, ovarian, lung, bladder, liver, and breast); CNS disorders (e.g., multiple sclerosis; ischemic brain injury and/or stroke, traumatic brain injury, neurodegenerative disorders (e.g., Parkinson's disease and Alzheimer's disease); AIDS-related dementia; and prion disease); cardiovascular disorders (e.g., atherosclerosis, myocarditis, cardiovascular disease, and

cardiopulmonary bypass complications); as well as many additional diseases, conditions, and disorders that are characterized by inflammation (e.g., hepatitis, rheumatoid arthritis, gout, trauma, pancreatitis, sarcoidosis, dermatitis, renal ischemia-reperfusion injury, Grave's disease, systemic lupus erythematosus, diabetes mellitus, and allogenic transplant rejection).

[0436] Because inflammation is a fundamental defense mechanism, inflammatory disorders can effect virtually any tissue of the body. Accordingly, polynucleotides, polypeptides, and antibodies of the invention, as well as agonists or antagonists thereof, have uses in the treatment of tissue-specific inflammatory disorders, including, but not limited to, adrenalitis, alveolitis, angiocholecystitis, appendicitis, balanitis, blepharitis, bronchitis, bursitis, carditis, cellulitis, cervicitis, cholecystitis, chorditis, cochlitis, colitis, conjunctivitis, cystitis, dermatitis, diverticulitis, encephalitis, endocarditis, esophagitis, eustachitis, fibrositis, folliculitis, gastritis, gastroenteritis, gingivitis, glossitis, hepatosplenitis, keratitis, labyrinthitis, laryngitis, lymphangitis, mastitis, media otitis, meningitis, metritis, mucitis, myocarditis, myosititis, myringitis, nephritis, neuritis, orchitis, osteochondritis, otitis, pericarditis, peritendonitis, peritonitis, pharyngitis, phlebitis, poliomyelitis, prostatitis, pulpitis, retinitis, rhinitis, salpingitis, scleritis, sclerochoroiditis, scrotitis, sinusitis, spondylitis, steatitis, stomatitis, synovitis, syringitis, tendonitis, tonsillitis, urethritis, and vaginitis.

[0437] In specific embodiments, polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, are useful to diagnose, prognose, prevent, and/or treat organ transplant rejections and graft-versus-host disease. Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. Polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, that inhibit an immune response, particularly the activation, proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing organ rejection or GVHD. In specific embodiments, polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, that inhibit an immune response, particularly the activation, proliferation, differentiation, or chemotaxis of T-cells, may be

an effective therapy in preventing experimental allergic and hyperacute xenograft rejection.

[0438] In other embodiments, polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, are useful to diagnose, prognose, prevent, and/or treat immune complex diseases, including, but not limited to, serum sickness, post streptococcal glomerulonephritis, polyarteritis nodosa, and immune complex-induced vasculitis.

[0439] Polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the invention can be used to treat, detect, and/or prevent infectious agents. For example, by increasing the immune response, particularly increasing the proliferation activation and/or differentiation of B and/or T cells, infectious diseases may be treated, detected, and/or prevented. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may also directly inhibit the infectious agent (refer to section of application listing infectious agents, etc), without necessarily eliciting an immune response.

[0440] In another embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a vaccine adjuvant that enhances immune responsiveness to an antigen. In a specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance tumor-specific immune responses.

[0441] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance anti-viral immune responses. Anti-viral immune responses that may be enhanced using the compositions of the invention as an adjuvant, include virus and virus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of: AIDS, meningitis, Dengue, EBV, and hepatitis (e.g., hepatitis B). In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of: HIV/AIDS, respiratory syncytial virus, Dengue, rotavirus, Japanese B encephalitis,

influenza A and B, parainfluenza, measles, cytomegalovirus, rabies, Junin, Chikungunya, Rift Valley Fever, herpes simplex, and yellow fever.

[0442] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance anti-bacterial or anti-fungal immune responses. Anti-bacterial or anti-fungal immune responses that may be enhanced using the compositions of the invention as an adjuvant, include bacteria or fungus and bacteria or fungus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: tetanus, Diphtheria, botulism, and meningitis type B.

[0443] In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: *Vibrio cholerae, Mycobacterium leprae, Salmonella typhi, Salmonella paratyphi, Meisseria meningitidis, Streptococcus pneumoniae*, Group B streptococcus, *Shigella spp.*, Enterotoxigenic *Escherichia coli,* Enterohemorrhagic *E. coli*, and *Borrelia burgdorferi.*

[0444] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an adjuvant to enhance anti-parasitic immune responses. Anti-parasitic immune responses that may be enhanced using the compositions of the invention as an adjuvant, include parasite and parasite associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a parasite. In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to Plasmodium (malaria) or Leishmania.

[0445] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may also be employed to treat infectious diseases including silicosis, sarcoidosis, and idiopathic pulmonary fibrosis; for example, by preventing the recruitment and activation of mononuclear phagocytes.

[0446] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an antigen for the

generation of antibodies to inhibit or enhance immune mediated responses against polypeptides of the invention.

[0447] In one embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are administered to an animal (e.g., mouse, rat, rabbit, hamster, guinea pig, pigs, micro-pig, chicken, camel, goat, horse, cow, sheep, dog, cat, non-human primate, and human, most preferably human) to boost the immune system to produce increased quantities of one or more antibodies (e.g., IgG, IgA, IgM, and IgE), to induce higher affinity antibody production and immunoglobulin class switching (e.g., IgG, IgA, IgM, and IgE), and/or to increase an immune response.

[0448] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a stimulator of B cell responsiveness to pathogens.

[0449] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an activator of T cells.

[0450] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent that elevates the immune status of an individual prior to their receipt of immunosuppressive therapies.

[0451] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to induce higher affinity antibodies.

[0452] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to increase serum immunoglobulin concentrations.

[0453] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to accelerate recovery of immunocompromised individuals.

[0454] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to boost immunoresponsiveness among aged populations and/or neonates.

[0455] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an immune system enhancer prior to, during, or after bone marrow transplant and/or other transplants (e.g.,

allogeneic or xenogeneic organ transplantation). With respect to transplantation, compositions of the invention may be administered prior to, concomitant with, and/or after transplantation. In a specific embodiment, compositions of the invention are administered after transplantation, prior to the beginning of recovery of T-cell populations. In another specific embodiment, compositions of the invention are first administered after transplantation after the beginning of recovery of T cell populations, but prior to full recovery of B cell populations.

[0456] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to boost immunoresponsiveness among individuals having an acquired loss of B cell function. Conditions resulting in an acquired loss of B cell function that may be ameliorated or treated by administering the polypeptides, antibodies, polynucleotides and/or agonists or antagonists thereof, include, but are not limited to, HIV Infection, AIDS, bone marrow transplant, and B cell chronic lymphocytic leukemia (CLL).

[0457] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to boost immunoresponsiveness among individuals having a temporary immune deficiency. Conditions resulting in a temporary immune deficiency that may be ameliorated or treated by administering the polypeptides, antibodies, polynucleotides and/or agonists or antagonists thereof, include, but are not limited to, recovery from viral infections (e.g., influenza), conditions associated with malnutrition, recovery from infectious mononucleosis, or conditions associated with stress, recovery from measles, recovery from blood transfusion, and recovery from surgery.

[0458] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a regulator of antigen presentation by monocytes, dendritic cells, and/or B-cells. In one embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention enhance antigen presentation or antagonizes antigen presentation in vitro or in vivo. Moreover, in related embodiments, said enhancement or antagonism of antigen presentation may be useful as an anti-tumor treatment or to modulate the immune system.

[0459] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as an agent to direct an

individual's immune system towards development of a humoral response (i.e. TH2) as opposed to a TH1 cellular response.

[0460] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means to induce tumor proliferation and thus make it more susceptible to anti-neoplastic agents. For example, multiple myeloma is a slowly dividing disease and is thus refractory to virtually all anti-neoplastic regimens. If these cells were forced to proliferate more rapidly their susceptibility profile would likely change.

[0461] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a stimulator of B cell production in pathologies such as AIDS, chronic lymphocyte disorder and/or Common Variable Immunodificiency.

[0462] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for generation and/or regeneration of lymphoid tissues following surgery, trauma or genetic defect. In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used in the pretreatment of bone marrow samples prior to transplant.

[0463] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a gene-based therapy for genetically inherited disorders resulting in immuno-incompetence/immunodeficiency such as observed among SCID patients.

[0464] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means of activating monocytes/macrophages to defend against parasitic diseases that effect monocytes such as Leishmania.

[0465] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means of regulating secreted cytokines that are elicited by polypeptides of the invention.

[0466] In another embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used in one or more of the applications decribed herein, as they may apply to veterinary medicine.

[0467] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means of blocking various aspects of immune responses to foreign agents or self. Examples of diseases or conditions in which blocking of certain aspects of immune responses may be desired include autoimmune disorders such as lupus, and arthritis, as well as immunoresponsiveness to skin allergies, inflammation, bowel disease, injury and diseases/disorders associated with pathogens.

[0468] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for preventing the B cell proliferation and Ig secretion associated with autoimmune diseases such as idiopathic thrombocytopenic purpura, systemic lupus erythematosus and multiple sclerosis.

[0469] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a inhibitor of B and/or T cell migration in endothelial cells. This activity disrupts tissue architecture or cognate responses and is useful, for example in disrupting immune responses, and blocking sepsis.

[0470] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for chronic hypergammaglobulinemia evident in such diseases as monoclonal gammopathy of undetermined significance (MGUS), Waldenstrom's disease, related idiopathic monoclonal gammopathies, and plasmacytomas.

[0471] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may be employed for instance to inhibit polypeptide chemotaxis and activation of macrophages and their precursors, and of neutrophils, basophils, B lymphocytes and some T-cell subsets, e.g., activated and CD8 cytotoxic T cells and natural killer cells, in certain autoimmune and chronic inflammatory and infective diseases. Examples of autoimmune diseases are described herein and include multiple sclerosis, and insulin-dependent diabetes.

[0472] The polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may also be employed to treat idiopathic hyper-eosinophilic syndrome by, for example, preventing eosinophil production and migration.

[0473] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used to enhance or inhibit complement mediated cell lysis.

[0474] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used to enhance or inhibit antibody dependent cellular cytotoxicity.

[0475] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may also be employed for treating atherosclerosis, for example, by preventing monocyte infiltration in the artery wall.

[0476] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may be employed to treat adult respiratory distress syndrome (ARDS).

[0477] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention may be useful for stimulating wound and tissue repair, stimulating angiogenesis, and/or stimulating the repair of vascular or lymphatic diseases or disorders. Additionally, agonists and antagonists of the invention may be used to stimulate the regeneration of mucosal surfaces.

[0478] In a specific embodiment, polynucleotides or polypeptides, and/or agonists thereof are used to diagnose, prognose, treat, and/or prevent a disorder characterized by primary or acquired immunodeficiency, deficient serum immunoglobulin production, recurrent infections, and/or immune system dysfunction. Moreover, polynucleotides or polypeptides, and/or agonists thereof may be used to treat or prevent infections of the joints, bones, skin, and/or parotid glands, blood-borne infections (e.g., sepsis, meningitis, septic arthritis, and/or osteomyelitis), autoimmune diseases (e.g., those disclosed herein), inflammatory disorders, and malignancies, and/or any disease or disorder or condition associated with these infections, diseases, disorders and/or malignancies) including, but not limited to, CVID, other primary immune deficiencies, HIV disease, CLL, recurrent bronchitis, sinusitis, otitis media, conjunctivitis, pneumonia, hepatitis, meningitis, herpes zoster (e.g., severe herpes zoster), and/or pneumocystis carnii. Other diseases and disorders that may be prevented, diagnosed, prognosed, and/or treated with polynucleotides or polypeptides, and/or agonists of the present invention include, but are

not limited to, HIV infection, HTLV-BLV infection, lymphopenia, phagocyte bactericidal dysfunction anemia, thrombocytopenia, and hemoglobinuria.

[0479] In another embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention are used to treat, and/or diagnose an individual having common variable immunodeficiency disease ("CVID"; also known as "acquired agammaglobulinemia" and "acquired hypogammaglobulinemia") or a subset of this disease.

[0480] In a specific embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to diagnose, prognose, prevent, and/or treat cancers or neoplasms including immune cell or immune tissue-related cancers or neoplasms. Examples of cancers or neoplasms that may be prevented, diagnosed, or treated by polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention include, but are not limited to, acute myelogenous leukemia, chronic myelogenous leukemia, Hodgkin's disease, non-Hodgkin's lymphoma, acute lymphocytic anemia (ALL) Chronic lymphocyte leukemia, plasmacytomas, multiple myeloma, Burkitt's lymphoma, EBV-transformed diseases, and/or diseases and disorders described in the section entitled "Hyperproliferative Disorders" elsewhere herein.

[0481] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a therapy for decreasing cellular proliferation of Large B-cell Lymphomas.

[0482] In another specific embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are used as a means of decreasing the involvement of B cells and Ig associated with Chronic Myelogenous Leukemia.

[0483] In specific embodiments, the compositions of the invention are used as an agent to boost immunoresponsiveness among B cell immunodeficient individuals, such as, for example, an individual who has undergone a partial or complete splenectomy.

[0484] Antagonists of the invention include, for example, binding and/or inhibitory antibodies, antisense nucleic acids, ribozymes or soluble forms of the polypeptides of the present invention (e.g., Fc fusion protein; see, e.g., Example 9). Agonists of the invention include, for example, binding or stimulatory antibodies, and soluble forms of the polypeptides (e.g., Fc fusion proteins; see, e.g., Example 9). Polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present

invention may be employed in a composition with a pharmaceutically acceptable carrier, e.g., as described herein.

[0485] In another embodiment, polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention are administered to an animal (including, but not limited to, those listed above, and also including transgenic animals) incapable of producing functional endogenous antibody molecules or having an otherwise compromised endogenous immune system, but which is capable of producing human immunoglobulin molecules by means of a reconstituted or partially reconstituted immune system from another animal (see, e.g., published PCT Application Nos. WO98/24893, WO/9634096, WO/9633735, and WO/9110741). Administration of polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention to such animals is useful for the generation of monoclonal antibodies against the polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the present invention.

Blood-Related Disorders

[0486] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to modulate hemostatic (the stopping of bleeding) or thrombolytic (clot dissolving) activity. For example, by increasing hemostatic or thrombolytic activity, polynucleotides or polypeptides, and/or agonists or antagonists of the present invention could be used to treat or prevent blood coagulation diseases, disorders, and/or conditions (e.g., afibrinogenemia, factor deficiencies, hemophilia), blood platelet diseases, disorders, and/or conditions (e.g., thrombocytopenia), or wounds resulting from trauma, surgery, or other causes. Alternatively, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention that can decrease hemostatic or thrombolytic activity could be used to inhibit or dissolve clotting. These molecules could be important in the treatment or prevention of heart attacks (infarction), strokes, or scarring.

[0487] In specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to prevent, diagnose, prognose, and/or treat thrombosis, arterial thrombosis, venous thrombosis, thromboembolism, pulmonary embolism, atherosclerosis, myocardial infarction, transient ischemic attack, unstable angina. In specific embodiments, the polynucleotides,

polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used for the prevention of occulsion of saphenous grafts, for reducing the risk of periprocedural thrombosis as might accompany angioplasty procedures, for reducing the risk of stroke in patients with atrial fibrillation including nonrheumatic atrial fibrillation, for reducing the risk of embolism associated with mechanical heart valves and or mitral valves disease. Other uses for the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention, include, but are not limited to, the prevention of occlusions in extrcorporeal devices (e.g., intravascular canulas, vascular access shunts in hemodialysis patients, hemodialysis machines, and cardiopulmonary bypass machines).

[0488] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to modulate hematopoietic activity (the formation of blood cells). For example, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to increase the quantity of all or subsets of blood cells, such as, for example, erythrocytes, lymphocytes (B or T cells), myeloid cells (e.g., basophils, eosinophils, neutrophils, mast cells, macrophages) and platelets. The ability to decrease the quantity of blood cells or subsets of blood cells may be useful in the prevention, detection, diagnosis and/or treatment of anemias and leukopenias described below. Alternatively, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to decrease the quantity of all or subsets of blood cells, such as, for example, erythrocytes, lymphocytes (B or T cells), myeloid cells (e.g., basophils, eosinophils, neutrophils, mast cells, macrophages) and platelets.. The ability to decrease the quantity of blood cells or subsets of blood cells may be useful in the prevention, detection, diagnosis and/or treatment of leukocytoses, such as, for example eosinophilia.

[0489] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to prevent, treat, or diagnose blood dyscrasia.

[0490] Anemias are conditions in which the number of red blood cells or amount of hemoglobin (the protein that carries oxygen) in them is below normal. Anemia may be caused by excessive bleeding, decreased red blood cell production, or increased red blood cell destruction (hemolysis). The polynucleotides, polypeptides, antibodies, and/or

agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing anemias. Anemias that may be treated prevented or diagnosed by the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention include iron deficiency anemia, hypochromic anemia, microcytic anemia, chlorosis, hereditary siderob;astic anemia, idiopathic acquired sideroblastic anemia, red cell aplasia, megaloblastic anemia (e.g., pernicious anemia, (vitamin B12 deficiency) and folic acid deficiency anemia), aplastic anemia, hemolytic anemias (e.g., autoimmune helolytic anemia, microangiopathic hemolytic anemia, and paroxysmal nocturnal hemoglobinuria). The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing anemias associated with diseases including but not limited to, anemias associated with systemic lupus erythematosus, cancers, lymphomas, chronic renal disease, and enlarged spleens. The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing anemias arising from drug treatments such as anemias associated with methyldopa, dapsone, and/or sulfadrugs. Additionally, rhe polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing anemias associated with abnormal red blood cell architecture including but not limited to, hereditary spherocytosis, hereditary elliptocytosis, glucose-6-phosphate dehydrogenase deficiency, and sickle cell anemia.

[0491] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing hemoglobin abnormalities, (e.g., those associated with sickle cell anemia, hemoglobin C disease, hemoglobin S-C disease, and hemoglobin E disease). Additionally, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating thalassemias, including, but not limited to major and minor forms of alpha-thalassemia and beta-thalassemia.

[0492] In another embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating bleeding disorders including, but not limited to, thrombocytopenia (e.g., idiopathic thrombocytopenic purpura, and thrombotic

thrombocytopenic purpura), Von Willebrand's disease, hereditary platelet disorders (e.g., storage pool disease such as Chediak-Higashi and Hermansky-Pudlak syndromes, thromboxane A2 dysfunction, thromboasthenia, and Bernard-Soulier syndrome), hemolytic-uremic syndrome, hemophelias such as hemophelia A or Factor VII deficiency and Christmas disease or Factor IX deficiency, Hereditary Hemorhhagic Telangiectsia, also known as Rendu-Osler-Weber syndrome, allergic purpura (Henoch Schonlein purpura) and disseminated intravascular coagulation.

[0493] The effect of the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention on the clotting time of blood may be monitored using any of the clotting tests known in the art including, but not limited to, whole blood partial thromboplastin time (PTT), the activated partial thromboplastin time (aPTT), the activated clotting time (ACT), the recalcified activated clotting time, or the Lee-White Clotting time.

[0494] Several diseases and a variety of drugs can cause platelet dysfunction. Thus, in a specific embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating acquired platelet dysfunction such as platelet dysfunction accompanying kidney failure, leukemia, multiple myeloma, cirrhosis of the liver, and systemic lupus erythematosus as well as platelet dysfunction associated with drug treatments, including treatment with aspirin, ticlopidine, nonsteroidal anti-inflammatory drugs (used for arthritis, pain, and sprains), and penicillin in high doses.

[0495] In another embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders characterized by or associated with increased or decreased numbers of white blood cells. Leukopenia occurs when the number of white blood cells decreases below normal. Leukopenias include, but are not limited to, neutropenia and lymphocytopenia. An increase in the number of white blood cells compared to normal is known as leukocytosis. The body generates increased numbers of white blood cells during infection. Thus, leukocytosis may simply be a normal physiological parameter that reflects infection. Alternatively, leukocytosis may be an indicator of injury or other disease such as cancer. Leokocytoses, include but are not limited to, eosinophilia, and accumulations of macrophages. In specific embodiments, the

polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating leukopenia. In other specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating leukocytosis

[0496] Leukopenia may be a generalized decreased in all types of white blood cells, or may be a specific depletion of particular types of white blood cells. Thus, in specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating decreases in neutrophil numbers, known as neutropenia. Neutropenias that may be diagnosed, prognosed, prevented, and/or treated by the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention include, but are not limited to, infantile genetic agranulocytosis, familial neutropenia, cyclic neutropenia, neutropenias resulting from or associated with dietary deficiencies (e.g., vitamin B 12 deficiency or folic acid deficiency), neutropenias resulting from or associated with drug treatments (e.g., antibiotic regimens such as penicillin treatment, sulfonamide treatment, anticoagulant treatment, anticonvulsant drugs, anti-thyroid drugs, and cancer chemotherapy), and neutropenias resulting from increased neutrophil destruction that may occur in association with some bacterial or viral infections, allergic disorders, autoimmune diseases, conditions in which an individual has an enlarged spleen (e.g., Felty syndrome, malaria and sarcoidosis), and some drug treatment regimens.

[0497] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating lymphocytopenias (decreased numbers of B and/or T lymphocytes), including, but not limited lymphocytopenias resulting from or associated with stress, drug treatments (e.g., drug treatment with corticosteroids, cancer chemotherapies, and/or radiation therapies), AIDS infection and/or other diseases such as, for example, cancer, rheumatoid arthritis, systemic lupus erythematosus, chronic infections, some viral infections and/or hereditary disorders (e.g., DiGeorge syndrome, Wiskott-Aldrich Syndome, severe combined immunodeficiency, ataxia telangiectsia).

[0498] The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing,

and/or treating diseases and disorders associated with macrophage numbers and/or macrophage function including, but not limited to, Gaucher's disease, Niemann-Pick disease, Letterer-Siwe disease and Hand-Schuller-Christian disease.

[0499] In another embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders associated with eosinophil numbers and/or eosinophil function including, but not limited to, idiopathic hypereosinophilic syndrome, eosinophilia-myalgia syndrome, and Hand-Schuller-Christian disease.

[0500] In yet another embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating leukemias and lymphomas including, but not limited to, acute lymphocytic (lymphpblastic) leukemia (ALL), acute myeloid (myelocytic, myelogenous, myeloblastic, or myelomonocytic) leukemia, chronic lymphocytic leukemia (e.g., B cell leukemias, T cell leukemias, Sezary syndrome, and Hairy cell leukenia), chronic myelocytic (myeloid, myelogenous, or granulocytic) leukemia, Hodgkin's lymphoma, non-hodgkin's lymphoma, Burkitt's lymphoma, and mycosis fungoides.

[0501] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in diagnosing, prognosing, preventing, and/or treating diseases and disorders of plasma cells including, but not limited to, plasma cell dyscrasias, monoclonal gammaopathies, monoclonal gammopathies of undetermined significance, multiple myeloma, macroglobulinemia, Waldenstrom's macroglobulinemia, cryoglobulinemia, and Raynaud's phenomenon.

[0502] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing myeloproliferative disorders, including but not limited to, polycythemia vera, relative polycythemia, secondary polycythemia, myelofibrosis, acute myelofibrosis, agnogenic myelod metaplasia, thrombocythemia, (including both primary and seconday thrombocythemia) and chronic myelocytic leukemia.

[0503] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as a treatment prior to surgery, to increase blood cell production.

[0504] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to enhance the migration, phagocytosis, superoxide production, antibody dependent cellular cytotoxicity of neutrophils, eosionophils and macrophages.

[0505] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to increase the number of stem cells in circulation prior to stem cells pheresis. In another specific embodiment, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to increase the number of stem cells in circulation prior to platelet pheresis.

[0506] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful as an agent to increase cytokine production.

[0507] In other embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in preventing, diagnosing, and/or treating primary hematopoietic disorders.

Hyperproliferative Disorders

[0508] Prostate cancer associated polynucleotides or polypeptides, or agonists or antagonists thereof, can be used to treat, prevent, diagnose and/or prognose hyperproliferative diseases, disorders, and/or conditions, including neoplasms.

[0509] In a specific embodiment, prostate cancer associated polynucleotides or polypeptides, or agonists or antagonists thereof, can be used to treat, prevent, and/or diagnose hyperproliferative diseases, disorders, and/or conditions of the prostate.

[0510] In a preferred embodiment, prostate cancer associated polynucleotides or polypeptides, or agonists or antagonists thereof, can be used to treat, prevent, and/or diagnose prostate neoplasms.

[0511] Prostate cancer associated polynucleotides or polypeptides, or agonists or antagonists of the invention, may inhibit the proliferation of the disorder through direct or indirect interactions. Alternatively, prostate cancer associated polynucleotides or polypeptides, or agonists or antagonists thereof, may proliferate other cells, which can inhibit the hyperproliferative disorder.

[0512] For example, by increasing an immune response, particularly increasing antigenic qualities of the hyperproliferative disorder or by proliferating, differentiating, or mobilizing T-cells, hyperproliferative diseases, disorders, and/or conditions can be treated, prevented, and/or diagnosed. This immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, decreasing an immune response may also be a method of treating, preventing, and/or diagnosing hyperproliferative diseases, disorders, and/or conditions, such as a chemotherapeutic agent.

[0513] Examples of hyperproliferative diseases, disorders, and/or conditions that can be treated, prevented, and/or diagnosed by prostate cancer associated polynucleotides or polypeptides, or agonists or antagonists thereof, include, but are not limited to neoplasms located in the: prostate, colon, abdomen, bone, breast, digestive system, liver, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, pelvic, skin, soft tissue, spleen, thoracic, and urogenital.

[0514] Similarly, other hyperproliferative disorders can also be treated or detected by polynucleotides or polypeptides, or agonists or antagonists of the present invention. Examples of such hyperproliferative disorders include, but are not limited to: Acute Childhood Lymphoblastic Leukemia, Acute Lymphoblastic Leukemia, Acute Lymphocytic Leukemia, Acute Myeloid Leukemia, Adrenocortical Carcinoma, Adult (Primary) Hepatocellular Cancer, Adult (Primary) Liver Cancer, Adult Acute Lymphocytic Leukemia, Adult Acute Myeloid Leukemia, Adult Hodgkin's Disease, Adult Hodgkin's Lymphoma, Adult Lymphocytic Leukemia, Adult Non-Hodgkin's Lymphoma, Adult Primary Liver Cancer, Adult Soft Tissue Sarcoma, AIDS-Related Lymphoma, AIDS-Related Malignancies, Anal Cancer, Astrocytoma, Bile Duct Cancer, Bladder Cancer, Bone Cancer, Brain Stem Glioma, Brain Tumors, Breast Cancer, Cancer of the Renal Pelvis and Ureter, Central Nervous System (Primary) Lymphoma, Central Nervous

System Lymphoma, Cerebellar Astrocytoma, Cerebral Astrocytoma, Cervical Cancer, Childhood (Primary) Hepatocellular Cancer, Childhood (Primary) Liver Cancer, Childhood Acute Lymphoblastic Leukemia, Childhood Acute Myeloid Leukemia, Childhood Brain Stem Glioma, Childhood Cerebellar Astrocytoma, Childhood Cerebral Astrocytoma, Childhood Extracranial Germ Cell Tumors, Childhood Hodgkin's Disease, Childhood Hodgkin's Lymphoma, Childhood Hypothalamic and Visual Pathway Glioma, Childhood Lymphoblastic Leukemia, Childhood Medulloblastoma, Childhood Non-Hodgkin's Lymphoma, Childhood Pineal and Supratentorial Primitive Neuroectodermal Tumors, Childhood Primary Liver Cancer, Childhood Rhabdomyosarcoma, Childhood Soft Tissue Sarcoma, Childhood Visual Pathway and Hypothalamic Glioma, Chronic Lymphocytic Leukemia, Chronic Myelogenous Leukemia, Colon Cancer, Cutaneous T-Cell Lymphoma, Endocrine Pancreas Islet Cell Carcinoma, Endometrial Cancer, Ependymoma, Epithelial Cancer, Esophageal Cancer, Ewing's Sarcoma and Related Tumors, Exocrine Pancreatic Cancer, Extracranial Germ Cell Tumor, Extragonadal Germ Cell Tumor, Extrahepatic Bile Duct Cancer, Eye Cancer, Female Breast Cancer, Gaucher's Disease, Gallbladder Cancer, Gastric Cancer, Gastrointestinal Carcinoid Tumor, Gastrointestinal Tumors, Germ Cell Tumors, Gestational Trophoblastic Tumor, Hairy Cell Leukemia, Head and Neck Cancer, Hepatocellular Cancer, Hodgkin's Disease, Hodgkin's Lymphoma, Hypergammaglobulinemia, Hypopharyngeal Cancer, Intestinal Cancers, Intraocular Melanoma, Islet Cell Carcinoma, Islet Cell Pancreatic Cancer, Kaposi's Sarcoma, Kidney Cancer, Laryngeal Cancer, Lip and Oral Cavity Cancer, Liver Cancer, Lung Cancer, Lymphoproliferative Disorders, Macroglobulinemia, Male Breast Cancer, Malignant Mesothelioma, Malignant Thymoma, Medulloblastoma, Melanoma, Mesothelioma, Metastatic Occult Primary Squamous Neck Cancer, Metastatic Primary Squamous Neck Cancer, Metastatic Squamous Neck Cancer, Multiple Myeloma, Multiple Myeloma/Plasma Cell Neoplasm, Myelodysplastic Syndrome, Myelogenous Leukemia, Myeloid Leukemia, Myeloproliferative Disorders, Nasal Cavity and Paranasal Sinus Cancer, Nasopharyngeal Cancer, Neuroblastoma, Non-Hodgkin's Lymphoma During Pregnancy, Nonmelanoma Skin Cancer, Non-Small Cell Lung Cancer, Occult Primary Metastatic Squamous Neck Cancer, Oropharyngeal Cancer, Osteo-/Malignant Fibrous Sarcoma, Osteosarcoma/Malignant Fibrous Histiocytoma, Osteosarcoma/Malignant Fibrous Histiocytoma of Bone, Ovarian Epithelial Cancer, Ovarian Germ Cell Tumor,

Ovarian Low Malignant Potential Tumor, Pancreatic Cancer, Paraproteinemias, Purpura, Parathyroid Cancer, Penile Cancer, Pheochromocytoma, Pituitary Tumor, Plasma Cell Neoplasm/Multiple Myeloma, Primary Central Nervous System Lymphoma, Primary Liver Cancer, Prostate Cancer, Rectal Cancer, Renal Cell Cancer, Renal Pelvis and Ureter Cancer, Retinoblastoma, Rhabdomyosarcoma, Salivary Gland Cancer, Sarcoidosis Sarcomas, Sezary Syndrome, Skin Cancer, Small Cell Lung Cancer, Small Intestine Cancer, Soft Tissue Sarcoma, Squamous Neck Cancer, Stomach Cancer, Supratentorial Primitive Neuroectodermal and Pineal Tumors, T-Cell Lymphoma, Testicular Cancer, Thymoma, Thyroid Cancer, Transitional Cell Cancer of the Renal Pelvis and Ureter, Transitional Renal Pelvis and Ureter Cancer, Trophoblastic Tumors, Ureter and Renal Pelvis Cell Cancer, Urethral Cancer, Uterine Cancer, Uterine Sarcoma, Vaginal Cancer, Visual Pathway and Hypothalamic Glioma, Vulvar Cancer, Waldenstrom's Macroglobulinemia, Wilms' Tumor, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

[0515] In another preferred embodiment, polynucleotides or polypeptides, or agonists or antagonists of the present invention are used to diagnose, prognose, prevent, and/or treat premalignant conditions and to prevent progression to a neoplastic or malignant state, including but not limited to those disorders described above. Such uses are indicated in conditions known or suspected of preceding progression to neoplasia or cancer, in particular, where non-neoplastic cell growth consisting of hyperplasia, metaplasia, or most particularly, dysplasia has occurred (for review of such abnormal growth conditions, see Robbins and Angell, 1976, Basic Pathology, 2d Ed., W. B. Saunders Co., Philadelphia, pp. 68-79.)

[0516] Hyperplasia is a form of controlled cell proliferation, involving an increase in cell number in a tissue or organ, without significant alteration in structure or function. Hyperplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention (including polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, angiofollicular mediastinal lymph node hyperplasia, angiolymphoid hyperplasia with eosinophilia, atypical melanocytic hyperplasia, basal cell hyperplasia, benign giant lymph node hyperplasia, cementum hyperplasia, congenital adrenal hyperplasia, congenital sebaceous hyperplasia, cystic hyperplasia, cystic hyperplasia of the breast, denture hyperplasia, ductal hyperplasia,

endometrial hyperplasia, fibromuscular hyperplasia, focal epithelial hyperplasia, gingival hyperplasia, inflammatory fibrous hyperplasia, inflammatory papillary hyperplasia, intravascular papillary endothelial hyperplasia, nodular hyperplasia of prostate, nodular regenerative hyperplasia, pseudoepitheliomatous hyperplasia, senile sebaceous hyperplasia, and verrucous hyperplasia.

[0517] Metaplasia is a form of controlled cell growth in which one type of adult or fully differentiated cell substitutes for another type of adult cell. Metaplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention (including polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, agnogenic myeloid metaplasia, apocrine metaplasia, atypical metaplasia, autoparenchymatous metaplasia, connective tissue metaplasia, epithelial metaplasia, intestinal metaplasia, metaplastic anemia, metaplastic ossification, metaplastic polyps, myeloid metaplasia, primary myeloid metaplasia, secondary myeloid metaplasia, squamous metaplasia, squamous metaplasia of amnion, and symptomatic myeloid metaplasia.

[0518] Dysplasia is frequently a forerunner of cancer, and is found mainly in the epithelia; it is the most disorderly form of non-neoplastic cell growth, involving a loss in individual cell uniformity and in the architectural orientation of cells. Dysplastic cells often have abnormally large, deeply stained nuclei, and exhibit pleomorphism. Dysplasia characteristically occurs where there exists chronic irritation or inflammation. Dysplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention (including polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, anhidrotic ectodermal dysplasia, anterofacial dysplasia, asphyxiating thoracic dysplasia, atriodigital dysplasia, bronchopulmonary dysplasia, cerebral dysplasia, cervical dysplasia, chondroectodermal dysplasia, cleidocranial dysplasia, congenital ectodermal dysplasia, craniodiaphysial dysplasia, craniocarpotarsal dysplasia, craniometaphysial dysplasia, dentin dysplasia, diaphysial dysplasia, ectodermal dysplasia, enamel dysplasia, encephalo-ophthalmic dysplasia, dysplasia epiphysialis hemimelia, dysplasia epiphysialis multiplex, dysplasia epiphysialis punctata, epithelial dysplasia, faciodigitogenital dysplasia, familial fibrous dysplasia of jaws, familial white folded dysplasia, fibromuscular dysplasia, fibrous dysplasia of bone, florid osseous dysplasia, hereditary renal-retinal dysplasia, hidrotic ectodermal dysplasia, hypohidrotic

ectodermal dysplasia, lymphopenic thymic dysplasia, mammary dysplasia, mandibulofacial dysplasia, metaphysial dysplasia, Mondini dysplasia, monostotic fibrous dysplasia, mucoepithelial dysplasia, multiple epiphysial dysplasia, oculoauriculovertebral dysplasia, oculodentodigital dysplasia, oculovertebral dysplasia, odontogenic dysplasia, ophthalmomandibulomelic dysplasia, periapical cemental dysplasia, polyostotic fibrous dysplasia, pseudoachondroplastic spondyloepiphysial dysplasia, retinal dysplasia, septo-optic dysplasia, spondyloepiphysial dysplasia, and ventriculoradial dysplasia.

[0519] Additional pre-neoplastic disorders which can be diagnosed, prognosed, prevented, and/or treated with compositions of the invention (including polynucleotides, polypeptides, agonists or antagonists) include, but are not limited to, benign dysproliferative disorders (e.g., benign tumors, fibrocystic conditions, tissue hypertrophy, intestinal polyps, colon polyps, and esophageal dysplasia), leukoplakia, keratoses, Bowen's disease, Farmer's Skin, solar cheilitis, and solar keratosis.

[0520] In another embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention conjugated to a toxin or a radioactive isotope, as described herein, may be used to treat cancers and neoplasms, including, but not limited to those described herein. In a further preferred embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention conjugated to a toxin or a radioactive isotope, as described herein, may be used to treat acute myelogenous leukemia.

[0521] Additionally, polynucleotides, polypeptides, and/or agonists or antagonists of the invention may affect apoptosis, and therefore, would be useful in treating a number of diseases associated with increased cell survival or the inhibition of apoptosis. For example, diseases associated with increased cell survival or the inhibition of apoptosis that could be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer, prostate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune disorders such as, multiple sclerosis,

Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection.

[0522] In preferred embodiments, polynucleotides, polypeptides, and/or agonists or antagonists of the invention are used to inhibit growth, progression, and/or metastasis of cancers, in particular those listed above.

[0523] Additional diseases or conditions associated with increased cell survival that could be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include, but are not limited to, progression, and/or metastases of malignancies and related disorders such as leukemia (including acute leukemias (e.g., acute lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (e.g., chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (e.g., Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, emangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma, and retinoblastoma.

[0524] Diseases associated with increased apoptosis that could be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, cerebellar degeneration and brain tumor or prior associated disease); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) myelodysplastic syndromes (such as aplastic anemia), graft v. host disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestosis (bile duct injury) and liver cancer); toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

[0525] Hyperproliferative diseases and/or disorders that could be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention, include, but are not limited to, neoplasms located in the liver, abdomen, bone, breast, digestive system, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous system (central and peripheral), lymphatic system, pelvis, skin, soft tissue, spleen, thorax, and urogenital tract.

[0526] Similarly, other hyperproliferative disorders can also be diagnosed, prognosed, prevented, and/or treated by polynucleotides, polypeptides, and/or agonists or antagonists of the invention. Examples of such hyperproliferative disorders include, but are not limited to: hypergammaglobulinemia, lymphoproliferative disorders, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenstron's macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

[0527] One preferred embodiment utilizes polynucleotides of the present invention to inhibit aberrant cellular division, by gene therapy using the present invention, and/or protein fusions or fragments thereof.

[0528] Thus, the present invention provides a method for treating cell proliferative diseases, disorders, and/or conditions by inserting into an abnormally proliferating cell a

polynucleotide of the present invention, wherein said polynucleotide represses said cell proliferation, disease, disorder, and/or condition.

[0529] In a preferred embodiment, the present invention provides a method for treating cell proliferative diseases, disorders and/or conditions of the prostate cancer by inserting into a cell, a polynucleotide of the present invention, wherein said polynucleotide represses said cell proliferation, disease and/or disorder.

[0530] Another embodiment of the present invention provides a method of treating cell-proliferative diseases, disorders, and/or conditions in individuals comprising administration of one or more active gene copies of the present invention to an abnormally proliferating cell or cells. In a preferred embodiment, polynucleotides of the present invention is a DNA construct comprising a recombinant expression vector effective in expressing a DNA sequence encoding said polynucleotides. In another preferred embodiment of the present invention, the DNA construct encoding the polynucleotides of the present invention is inserted into cells to be treated utilizing a retrovirus, or more preferably an adenoviral vector (see, e.g., G J. Nabel, et. al., PNAS 96: 324-326 (1999), which is hereby incorporated by reference). In a most preferred embodiment, the viral vector is defective and will not transform non-proliferating cells, only proliferating cells. Moreover, in a preferred embodiment, the polynucleotides of the present invention inserted into proliferating cells either alone, or in combination with or fused to other polynucleotides, can then be modulated via an external stimulus (i.e., magnetic, specific small molecule, chemical, or drug administration, etc.), which acts upon the promoter upstream of said polynucleotides to induce expression of the encoded protein product. As such the beneficial therapeutic affect of the present invention may be expressly modulated (i.e., to increase, decrease, or inhibit expression of the present invention) based upon said external stimulus.

[0531] Polynucleotides of the present invention may be useful in repressing expression of oncogenic genes or antigens. By "repressing expression of the oncogenic genes " is intended the suppression of the transcription of the gene, the degradation of the gene transcript (pre-message RNA), the inhibition of splicing, the destruction of the messenger RNA, the prevention of the post-translational modifications of the protein, the destruction of the protein, or the inhibition of the normal function of the protein.

[0532] For local administration to abnormally proliferating cells, polynucleotides of the present invention may be administered by any method known to those of skill in the art including, but not limited to transfection, electroporation, microinjection of cells, or in vehicles such as liposomes, lipofectin, or as naked polynucleotides, or any other method described throughout the specification. The polynucleotide of the present invention may be delivered by known gene delivery systems such as, but not limited to, retroviral vectors (Gilboa, J. Virology 44:845 (1982); Hocke, Nature 320:275 (1986); Wilson, et al., Proc. Natl. Acad. Sci. U.S.A. 85:3014), vaccinia virus system (Chakrabarty et al., Mol. Cell Biol. 5:3403 (1985) or other efficient DNA delivery systems (Yates et al., Nature 313:812 (1985)) known to those skilled in the art. These references are exemplary only and are hereby incorporated by reference. In order to specifically deliver or transfect cells which are abnormally proliferating and spare non-dividing cells, it is preferable to utilize a retrovirus, or adenoviral (as described in the art and elsewhere herein) delivery system known to those of skill in the art. Since host DNA replication is required for retroviral DNA to integrate and the retrovirus will be unable to self replicate due to the lack of the retrovirus genes needed for its life cycle. Utilizing such a retroviral delivery system for polynucleotides of the present invention will target said gene and constructs to abnormally proliferating cells and will spare the non-dividing normal cells.

[0533] The polynucleotides of the present invention may be delivered directly to cell proliferative disorder/disease sites in internal organs, body cavities and the like by use of imaging devices used to guide an injecting needle directly to the disease site. The polynucleotides of the present invention may also be administered to disease sites at the time of surgical intervention.

[0534] By "cell proliferative disease" is meant any human or animal disease or disorder, affecting any one or any combination of organs, cavities, or body parts, which is characterized by single or multiple local abnormal proliferations of cells, groups of cells, or tissues, whether benign or malignant.

[0535] Any amount of the polynucleotides of the present invention may be administered as long as it has a biologically inhibiting effect on the proliferation of the treated cells. Moreover, it is possible to administer more than one of the polynucleotide of the present invention simultaneously to the same site. By "biologically inhibiting" is meant partial or total growth inhibition as well as decreases in the rate of proliferation or

growth of the cells. The biologically inhibitory dose may be determined by assessing the effects of the polynucleotides of the present invention on target malignant or abnormally proliferating cell growth in tissue culture, tumor growth in animals and cell cultures, or any other method known to one of ordinary skill in the art.

[0536] The present invention is further directed to antibody-based therapies which involve administering of anti-polypeptides and anti-polynucleotide antibodies to a mammalian, preferably human, patient for treating one or more of the described diseases, disorders, and/or conditions. Methods for producing anti-polypeptides and anti-polynucleotide antibodies polyclonal and monoclonal antibodies are described in detail elsewhere herein. Such antibodies may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

[0537] A summary of the ways in which the antibodies of the present invention may be used therapeutically includes binding polynucleotides or polypeptides of the present invention locally or systemically in the body or by direct cytotoxicity of the antibody, e.g., as mediated by complement (CDC) or by effector cells (ADCC). Some of these approaches are described in more detail below. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of the present invention for diagnostic, monitoring or therapeutic purposes without undue experimentation.

[0538] In particular, the antibodies, fragments and derivatives of the present invention are useful for treating a subject having or developing cell proliferative and/or differentiation diseases, disorders, and/or conditions as described herein. Such treatment comprises administering a single or multiple doses of the antibody, or a fragment, derivative, or a conjugate thereof.

[0539] The antibodies of this invention may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors, for example, which serve to increase the number or activity of effector cells which interact with the antibodies.

[0540] It is preferred to use high affinity and/or potent *in vivo* inhibiting and/or neutralizing antibodies against polypeptides or polynucleotides of the present invention, fragments or regions thereof, for both immunoassays directed to and therapy of diseases, disorders, and/or conditions related to polynucleotides or polypeptides, including

fragments thereof, of the present invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides, including fragments thereof. Preferred binding affinities include those with a dissociation constant or Kd less than $5X10^{-6}$M, 10^{-6}M, $5X10^{-7}$M, 10^{-7}M, $5X10^{-8}$M, 10^{-8}M, $5X10^{-9}$M, 10^{-9}M, $5X10^{-10}$M, 10^{-10}M, $5X10^{-11}$M, 10^{-11}M, $5X10^{-12}$M, 10^{-12}M, $5X10^{-13}$M, 10^{-13}M, $5X10^{-14}$M, 10^{-14}M, $5X10^{-15}$M, and 10^{-15}M.

[0541] Moreover, prostate cancer antigen polypeptides of the present invention or fragments thereof, are useful in inhibiting the angiogenesis of proliferative cells or tissues, either alone, as a protein fusion, or in combination with other polypeptides directly or indirectly, as described elsewhere herein. In a most preferred embodiment, said anti-angiogenesis effect may be achieved indirectly, for example, through the inhibition of hematopoietic, tumor-specific cells, such as tumor-associated macrophages (see, e.g., Joseph IB, et al. J Natl Cancer Inst, 90(21):1648-53 (1998), which is hereby incorporated by reference). Antibodies directed to polypeptides or polynucleotides of the present invention may also result in inhibition of angiogenesis directly, or indirectly (see, e.g., Witte L, et al., Cancer Metastasis Rev. 17(2):155-61 (1998), which is hereby incorporated by reference)).

[0542] Polypeptides, including protein fusions, of the present invention, or fragments thereof may be useful in inhibiting proliferative cells or tissues through the induction of apoptosis. Said polypeptides may act either directly, or indirectly to induce apoptosis of proliferative cells and tissues, for example in the activation of a death-domain receptor, such as tumor necrosis factor (TNF) receptor-1, CD95 (Fas/APO-1), TNF-receptor-related apoptosis-mediated protein (TRAMP) and TNF-related apoptosis-inducing ligand (TRAIL) receptor-1 and -2 (see, e.g., Schulze-Osthoff K, et.al., Eur J Biochem 254(3):439-59 (1998), which is hereby incorporated by reference). Moreover, in another preferred embodiment of the present invention, said polypeptides may induce apoptosis through other mechanisms, such as in the activation of other proteins which will activate apoptosis, or through stimulating the expression of said proteins, either alone or in combination with small molecule drugs or adjuvants, such as apoptonin, galectins, thioredoxins, antiinflammatory proteins (See for example, Mutat. Res. 400(1-2):447-55 (1998), Med Hypotheses.50(5):423-33 (1998), Chem. Biol. Interact. Apr 24;111-112:23-

34 (1998), J. Mo. Med. 76(6):402-12 (1998), Int. J. Tissue React. 20(1):3-15 (1998), which are all hereby incorporated by reference).

[0543] Polypeptides, including protein fusions to, or fragments thereof, of the present invention are useful in inhibiting the metastasis of proliferative cells or tissues. Inhibition may occur as a direct result of administering polypeptides, or antibodies directed to said polypeptides as described elsewhere herein, or indirectly, such as activating the expression of proteins known to inhibit metastasis, for example alpha 4 integrins, (See, e.g., Curr Top Microbiol Immunol 1998;231:125-41, which is hereby incorporated by reference). Such therapeutic affects of the present invention may be achieved either alone, or in combination with small molecule drugs or adjuvants.

[0544] In another embodiment, the invention provides a method of delivering compositions containing the polypeptides of the invention (e.g., compositions containing polypeptides or anti- prostate cancer antigen polypeptide antibodies associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs) to targeted cells expressing the polypeptide of the present invention. prostate cancer antigen polypeptides or anti- prostate cancer antigen polypeptide antibodies of the invention may be associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs via hydrophobic, hydrophilic, ionic and/or covalent interactions.

[0545] Polypeptides, protein fusions to, or fragments thereof, of the present invention are useful in enhancing the immunogenicity and/or antigenicity of proliferating cells or tissues, either directly, such as would occur if the polypeptides of the present invention 'vaccinated' the immune response to respond to proliferative antigens and immunogens, or indirectly, such as in activating the expression of proteins known to enhance the immune response (e.g. chemokines), to said antigens and immunogens.

<u>Urinary System Disorders</u>

[0546] Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention, may be used to treat, prevent, diagnose, and/or prognose disorders of the urinary system, including but not limited to disorders of the renal system, bladder, ureters, and urethra. Renal disorders include, but are not limited to, kidney failure, nephritis, blood vessel disorders of kidney, metabolic and congenital kidney disorders,

urinary disorders of the kidney, autoimmune disorders, sclerosis and necrosis, electrolyte imbalance, and kidney cancers.

[0547] Kidney failure diseases include, but are not limited to, acute kidney failure, chronic kidney failure, atheroembolic renal failure, and end-stage renal disease. Inflammatory diseases of the kidney include acute glomerulonephritis, postinfectious glomerulonephritis, rapidly progressive glomerulonephritis, nephrotic syndrome, membranous glomerulonephritis, familial nephrotic syndrome, membranoproliferative glomerulonephritis I and II, mesangial proliferative glomerulonephritis, chronic glomerulonephritis, acute tubulointerstitial nephritis, chronic tubulointerstitial nephritis, acute post-streptococcal glomerulonephritis (PSGN), pyelonephritis, lupus nephritis, chronic nephritis, interstitial nephritis, and post-streptococcal glomerulonephritis.

[0548] Blood vessel disorders of the kidneys include, but are not limited to, kidney infarction, atheroembolic kidney disease, cortical necrosis, malignant nephrosclerosis, renal vein thrombosis, renal underperfusion, renal ischemia-reperfusion, renal artery embolism, and renal artery stenosis. Kidney disorders resulting form urinary tract problems include, but are not limited to, pyelonephritis, hydronephrosis, urolithiasis (renal lithiasis, nephrolithiasis), reflux nephropathy, urinary tract infections, urinary retention, and acute or chronic unilateral obstructive uropathy.

[0549] Metabolic and congenital disorders of the kidneys include, but are not limited to, renal tubular acidosis, renal glycosuria, nephrogenic diabetes insipidus, cystinuria, Fanconi's syndrome, vitamin D-resistant rickets, Hartnup disease, Bartter's syndrome, Liddle's syndrome, polycystic kidney disease, medullary cystic disease, medullary sponge kidney, Alport's syndrome, nail-patella syndrome, congenital nephrotic syndrome, CRUSH syndrome, horseshoe kidney, diabetic nephropathy, nephrogenic diabetes insipidus, analgesic nephropathy, kidney stones, and membranous nephropathy, Kidney disorders resulting from an autoimmune response include, but are not limited to, systemic lupus erythematosus (SLE), Goodpasture syndrome, IgA nephropathy, and IgM mesangial proliferative glomerulonephritis.

[0550] Sclerotic or necrotic disorders of the kidney include, but are not limited to, glomerulosclerosis, diabetic nephropathy, focal segmental glomerulosclerosis (FSGS), necrotizing glomerulonephritis, and renal papillary necrosis. Kidneys may also develop

carcinomas, including, but not limited to, hypernephroma, nephroblastoma, renal cell cancer, transitional cell cancer, squamous cell cancer, and Wilm's tumor.

[0551] Kidney disorders may also result in electrolyte imbalances, including, but not limited to, nephrocalcinosis, pyuria, edema, hydronephritis, proteinuria, hyponatremia, hypernatremia, hypokalemia, hyperkalemia, hypocalcemia, hypercalcemia, hypophosphatemia, and hyperphosphatemia.

[0552] Bladder disorders include, but are not limited to, benign prostatic hyperplasia (BPH), interstitial cystitis (IC), prostatitis, proteinuria, urinary tract infections, urinary incontinence, urinary retention. Disorders of the ureters and urethra include, but are not limited to, acute or chronic unilateral obstructive uropathy. The bladder, ureters, and urethra may also develop carcinomas, including, but not limited to, superficial bladder canccer, invasive bladder cancer, carcinoma of the ureter, and urethra cancers.

[0553] Polypeptides may be administered using any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, biolistic injectors, particle accelerators, gelfoam sponge depots, other commercially available depot materials, osmotic pumps, oral or suppositorial solid pharmaceutical formulations, decanting or topical applications during surgery, aerosol delivery. Such methods are known in the art. Polypeptides may be administered as part of a Therapeutic, described in more detail below. Methods of delivering polynucleotides are described in more detail herein.

Cardiovascular Disorders

[0554] Polynucleotides or polypeptides, or agonists or antagonists of the present invention, may be used to treat, prevent, diagnose, and/or prognose cardiovascular disorders, including, but not limited to, peripheral artery disease, such as limb ischemia.

[0555] Cardiovascular disorders include cardiovascular abnormalities, such as arterio-arterial fistula, arteriovenous fistula, cerebral arteriovenous malformations, congenital heart defects, pulmonary atresia, and Scimitar Syndrome. Congenital heart defects include aortic coarctation, cor triatriatum, coronary vessel anomalies, crisscross heart, dextrocardia, patent ductus arteriosus, Ebstein's anomaly, Eisenmenger complex, hypoplastic left heart syndrome, levocardia, tetralogy of fallot, transposition of great vessels, double outlet right ventricle, tricuspid atresia, persistent truncus arteriosus, total

anomalous pulmonary venous connection, hypoplastic left heart syndrome, and heart septal defects, such as aortopulmonary septal defect, endocardial cushion defects, Lutembacher's Syndrome, atrioventricular canal defect, trilogy of Fallot, ventricular heart septal defects.

[0556] Cardiovascular disorders also include heart disease, such as arrhythmias, carcinoid heart disease, high cardiac output, low cardiac output, cardiac tamponade, endocarditis (including bacterial), heart aneurysm, cardiac arrest, sudden cardiac death, congestive heart failure, congestive cardiomyopathy, paroxysmal dyspnea, cardiac edema, heart hypertrophy, congestive cardiomyopathy, left ventricular hypertrophy, right ventricular hypertrophy, post-infarction heart rupture, ventricular septal rupture, heart valve diseases, myocardial diseases, myocardial ischemia, pericardial effusion, pericarditis (including constrictive and tuberculous), pneumopericardium, postpericardiotomy syndrome, pulmonary heart disease, rheumatic heart disease, ventricular dysfunction, hyperemia, cardiovascular pregnancy complications, Scimitar Syndrome, diastolic dysfunction, enlarged heart, heart block, J-curve phenomenon, rheumatic heart disease, Marfan syndrome, cardiovascular syphilis, and cardiovascular tuberculosis.

[0557] Arrhythmias include sinus arrhythmia, atrial fibrillation, atrial flutter, bradycardia, extrasystole, Adams-Stokes Syndrome, bundle-branch block, sinoatrial block, long QT syndrome, parasystole, Lown-Ganong-Levine Syndrome, Mahaim-type pre-excitation syndrome, Wolff-Parkinson-White syndrome, sick sinus syndrome, tachycardias, and ventricular fibrillation. Tachycardias include paroxysmal tachycardia, supraventricular tachycardia, accelerated idioventricular rhythm, atrioventricular nodal reentry tachycardia, ectopic atrial tachycardia, ectopic junctional tachycardia, sinoatrial nodal reentry tachycardia, sinus tachycardia, Torsades de Pointes, and ventricular tachycardia.

[0558] Heart valve disease include aortic valve insufficiency, aortic valve stenosis, heart murmurs, aortic valve prolapse, mitral valve prolapse, tricuspid valve prolapse, mitral valve insufficiency, mitral valve stenosis, pulmonary atresia, pulmonary valve insufficiency, pulmonary valve stenosis, tricuspid atresia, tricuspid valve insufficiency, tricuspid valve stenosis, and bicuspid aortic valve.

[0559] Myocardial diseases include alcoholic cardiomyopathy, congestive cardiomyopathy, hypertrophic cardiomyopathy, aortic subvalvular stenosis, pulmonary

subvalvular stenosis, restrictive cardiomyopathy, Chagas cardiomyopathy, endocardial fibroelastosis, endomyocardial fibrosis, Kearns Syndrome, Barth syndrome, myocardial reperfusion injury, and myocarditis.

[0560] Myocardial ischemias include coronary disease, such as angina pectoris, Prinzmetal's angina, unstable angina, coronary aneurysm, coronary arteriosclerosis, coronary thrombosis, coronary vasospasm, myocardial infarction and myocardial stunning.

[0561] Cardiovascular diseases also include vascular diseases such as aneurysms, angiodysplasia, angiomatosis, bacillary angiomatosis, Hippel-Lindau Disease, Klippel-Trenaunay-Weber Syndrome, Sturge-Weber Syndrome, angioneurotic edema, aortic diseases, Takayasu's Arteritis, aortitis, Leriche's Syndrome, arterial occlusive diseases, arteritis, enarteritis, polyarteritis nodosa, cerebrovascular disorders, diabetic angiopathies, diabetic retinopathy, embolisms, thrombosis, erythromelalgia, hemorrhoids, hepatic veno-occlusive disease, hypertension, hypotension (shock), ischemia, peripheral vascular diseases, phlebitis, superficial phlebitis, pulmonary veno-occlusive disease, chronic obstructive pulmonary disease, Buerger's disease, Raynaud's disease, CREST syndrome, retinal vein occlusion, Scimitar syndrome, superior vena cava syndrome, telangiectasia, atacia telangiectasia, hereditary hemorrhagic telangiectasia, deep vein thrombosis, varicocele, varicose veins, varicose ulcer, vasculitis, and venous insufficiency.

[0562] Aneurysms include dissecting aneurysms, false aneurysms, infected aneurysms, ruptured aneurysms, aortic aneurysms, cerebral aneurysms, coronary aneurysms, heart aneurysms, and iliac aneurysms.

[0563] Arterial occlusive diseases include arteriosclerosis, arteriolosclerosis, atherosclerosis, intermittent claudication, carotid stenosis, fibromuscular dysplasias, mesenteric vascular occlusion, Moyamoya disease, renal artery obstruction, retinal artery occlusion, and thromboangiitis obliterans.

[0564] Cerebrovascular disorders include carotid artery diseases, cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformation, cerebral artery diseases, cerebral embolism and thrombosis, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, cerebral hemorrhage, epidural hematoma, subdural hematoma, subaraxhnoid hemorrhage, cerebral infarction, cerebral ischemia (including transient), subclavian steal syndrome, periventricular

leukomalacia, vascular headache, cluster headache, migraine, and vertebrobasilar insufficiency.

[0565] Embolisms include air embolisms, amniotic fluid embolisms, cholesterol embolisms, blue toe syndrome, fat embolisms, pulmonary embolisms, and thromoboembolisms. Thrombosis include coronary thrombosis, hepatic vein thrombosis, deep vein thrombosis, retinal vein occlusion, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, and thrombophlebitis.

[0566] Ischemia includes cerebral ischemia, ischemic colitis, silent ischemia, compartment syndromes, anterior compartment syndrome, myocardial ischemia, reperfusion injuries, and peripheral limb ischemia. Vasculitis includes aortitis, arteritis, Behcet's Syndrome, Churg-Strauss Syndrome, mucocutaneous lymph node syndrome, thromboangiitis obliterans, hypersensitivity vasculitis, Schoenlein-Henoch purpura, allergic cutaneous vasculitis, and Wegener's granulomatosis.

[0567] Cardiovascular diseases can also occur due to electrolyte imbalances that include, but are not limited to hyponatremia, hypernatremia, hypokalemia, hyperkalemia, hypocalcemia, hypercalcemia, hypophosphatemia, and hyperphophatemia. Neoplasm and/or cancers of the cardiovascular system include, but are not limited to, myxomas, fibromas, and rhabdomyomas.

[0568] Polypeptides may be administered using any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, biolistic injectors, particle accelerators, gelfoam sponge depots, other commercially available depot materials, osmotic pumps, oral or suppositorial solid pharmaceutical formulations, decanting or topical applications during surgery, aerosol delivery. Such methods are known in the art. Polypeptides may be administered as part of a Therapeutic, described in more detail below. Methods of delivering polynucleotides are described in more detail herein.

Respiratory Disorders

[0569] Polynucleotides or polypeptides, or agonists or antagonists of the present invention may be used to treat, prevent, diagnose, and/or prognose diseases and/or disorders of the respiratory system.

[0570] Diseases and disorders of the respiratory system include, but are not limited to, nasal vestibulitis, nonallergic rhinitis (e.g., acute rhinitis, chronic rhinitis, atrophic rhinitis, vasomotor rhinitis), nasal polyps, and sinusitis, juvenile angiofibromas, cancer of the nose and juvenile papillomas, vocal cord polyps, nodules (singer's nodules), contact ulcers, vocal cord paralysis, laryngoceles, pharyngitis (e.g., viral and bacterial), tonsillitis, tonsillar cellulitis, parapharyngeal abscess, laryngitis, laryngoceles, and throat cancers (e.g., cancer of the nasopharynx, tonsil cancer, larynx cancer), lung cancer (e.g., squamous cell carcinoma, small cell (oat cell) carcinoma, large cell carcinoma, and adenocarcinoma), allergic disorders (eosinophilic pneumonia, hypersensitivity pneumonitis (e.g., extrinsic allergic alveolitis, allergic interstitial pneumonitis, organic dust pneumoconiosis, allergic bronchopulmonary aspergillosis, asthma, Wegener's granulomatosis (granulomatous vasculitis), Goodpasture's syndrome)), pneumonia (e.g., bacterial pneumonia (e.g., *Streptococcus pneumoniae* (pneumoncoccal pneumonia), *Staphylococcus aureus* (staphylococcal pneumonia), Gram-negative bacterial pneumonia (caused by, e.g., *Klebsiella* and *Pseudomas spp.*), *Mycoplasma pneumoniae* pneumonia, *Hemophilus influenzae* pneumonia, *Legionella pneumophila* (Legionnaires' disease), and *Chlamydia psittaci* (Psittacosis)), and viral pneumonia (e.g., influenza, chickenpox (varicella).

[0571] Additional diseases and disorders of the respiratory system include, but are not limited to bronchiolitis, polio (poliomyelitis), croup, respiratory syncytial viral infection, mumps, erythema infectiosum (fifth disease), roseola infantum, progressive rubella panencephalitis, german measles, and subacute sclerosing panencephalitis), fungal pneumonia (e.g., Histoplasmosis, Coccidioidomycosis, Blastomycosis, fungal infections in people with severely suppressed immune systems (e.g., cryptococcosis, caused by *Cryptococcus neoformans*; aspergillosis, caused by *Aspergillus spp.*; candidiasis, caused by *Candida*; and mucormycosis)), *Pneumocystis carinii* (pneumocystis pneumonia), atypical pneumonias (e.g., *Mycoplasma* and *Chlamydia* spp.), opportunistic infection pneumonia, nosocomial pneumonia, chemical pneumonitis, and aspiration pneumonia, pleural disorders (e.g., pleurisy, pleural effusion, and pneumothorax (e.g., simple spontaneous pneumothorax, complicated spontaneous pneumothorax, tension pneumothorax)), obstructive airway diseases (e.g., asthma, chronic obstructive pulmonary disease (COPD), emphysema, chronic or acute bronchitis), occupational lung diseases

(e.g., silicosis, black lung (coal workers' pneumoconiosis), asbestosis, berylliosis, occupational asthsma, byssinosis, and benign pneumoconioses), Infiltrative Lung Disease (e.g., pulmonary fibrosis (e.g., fibrosing alveolitis, usual interstitial pneumonia), idiopathic pulmonary fibrosis, desquamative interstitial pneumonia, lymphoid interstitial pneumonia, histiocytosis X (e.g., Letterer-Siwe disease, Hand-Schüller-Christian disease, eosinophilic granuloma), idiopathic pulmonary hemosiderosis, sarcoidosis and pulmonary alveolar proteinosis), Acute respiratory distress syndrome (also called, e.g., adult respiratory distress syndrome), edema, pulmonary embolism, bronchitis (e.g., viral, bacterial), bronchiectasis, atelectasis, lung abscess (caused by, e.g., *Staphylococcus aureus* or *Legionella pneumophila*), and cystic fibrosis.

Anti-Angiogenesis Activity

[0572] The naturally occurring balance between endogenous stimulators and inhibitors of angiogenesis is one in which inhibitory influences predominate. Rastinejad *et al., Cell 56*:345-355 (1989). In those rare instances in which neovascularization occurs under normal physiological conditions, such as wound healing, organ regeneration, embryonic development, and female reproductive processes, angiogenesis is stringently regulated and spatially and temporally delimited. Under conditions of pathological angiogenesis such as that characterizing solid tumor growth, these regulatory controls fail. Unregulated angiogenesis becomes pathologic and sustains progression of many neoplastic and non-neoplastic diseases. A number of serious diseases are dominated by abnormal neovascularization including solid tumor growth and metastases, arthritis, some types of eye disorders, and psoriasis. See, e.g., reviews by Moses *et al., Biotech. 9*:630-634 (1991); Folkman *et al., N. Engl. J. Med., 333*:1757-1763 (1995); Auerbach *et al., J. Microvasc. Res. 29*:401-411 (1985); Folkman, Advances in Cancer Research, eds. Klein and Weinhouse, Academic Press, New York, pp. 175-203 (1985); Patz, *Am. J. Opthalmol. 94*:715-743 (1982); and Folkman *et al.,* Science *221*:719-725 (1983). In a number of pathological conditions, the process of angiogenesis contributes to the disease state. For example, significant data have accumulated which suggest that the growth of solid tumors is dependent on angiogenesis. Folkman and Klagsbrun, *Science 235*:442-447 (1987).

[0573] The polynucleotides encoding a polypeptide of the present invention may

be administered along with other polynucleotides encoding an angiogenic protein. Examples of angiogenic proteins include, but are not limited to, acidic and basic fibroblast growth factors, VEGF-1, VEGF-2, VEGF-3, epidermal growth factor alpha and beta, platelet-derived endothelial cell growth factor, platelet-derived growth factor, tumor necrosis factor alpha, hepatocyte growth factor, insulin like growth factor, colony stimulating factor, macrophage colony stimulating factor, granulocyte/macrophage colony stimulating factor, and nitric oxide synthase.

[0574] The present invention provides for treatment of diseases or disorders associated with neovascularization by administration of the polynucleotides and/or polypeptides of the invention, as well as agonists or antagonists of the present invention. Malignant and metastatic conditions which can be treated with the polynucleotides and polypeptides, or agonists or antagonists of the invention include, but are not limited to, malignancies, solid tumors, and cancers described herein and otherwise known in the art (for a review of such disorders, see Fishman *et al.,* Medicine, 2d Ed., J. B. Lippincott Co., Philadelphia (1985)).Thus, the present invention provides a method of treating an angiogenesis-related disease and/or disorder, comprising administering to an individual in need thereof a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist of the invention. For example, polynucleotides, polypeptides, antagonists and/or agonists may be utilized in a variety of additional methods in order to therapeutically treat a cancer or tumor. Cancers which may be treated with polynucleotides, polypeptides, antagonists and/or agonists include, but are not limited to solid tumors, including prostate, lung, breast, ovarian, stomach, pancreas, larynx, esophagus, testes, liver, parotid, biliary tract, colon, rectum, cervix, uterus, endometrium, kidney, bladder, thyroid cancer; primary tumors and metastases; melanomas; glioblastoma; Kaposi's sarcoma; leiomyosarcoma; non- small cell lung cancer; colorectal cancer; advanced malignancies; and blood born tumors such as leukemias. For example, polynucleotides, polypeptides, antagonists and/or agonists may be delivered topically, in order to treat cancers such as skin cancer, head and neck tumors, breast tumors, and Kaposi's sarcoma.

[0575] Within yet other aspects, polynucleotides, polypeptides, antagonists and/or agonists may be utilized to treat superficial forms of bladder cancer by, for example, intravesical administration. Polynucleotides, polypeptides, antagonists and/or agonists

may be delivered directly into the tumor, or near the tumor site, via injection or a catheter. Of course, as the artisan of ordinary skill will appreciate, the appropriate mode of administration will vary according to the cancer to be treated. Other modes of delivery are discussed herein.

[0576] Polynucleotides, polypeptides, antagonists and/or agonists may be useful in treating other disorders, besides cancers, which involve angiogenesis. These disorders include, but are not limited to: benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; artheroscleric plaques; ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, uvietis and Pterygia (abnormal blood vessel growth) of the eye; rheumatoid arthritis; psoriasis; delayed wound healing; endometriosis; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; Osler-Webber Syndrome; plaque neovascularization; telangiectasia; hemophiliac joints; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and atherosclerosis.

[0577] For example, within one aspect of the present invention methods are provided for treating hypertrophic scars and keloids, comprising the step of administering a polynucleotide, polypeptide, antagonist and/or agonist of the invention to a hypertrophic scar or keloid.

[0578] Within one embodiment of the present invention polynucleotides, polypeptides, antagonists and/or agonists are directly injected into a hypertrophic scar or keloid, in order to prevent the progression of these lesions. This therapy is of particular value in the prophylactic treatment of conditions which are known to result in the development of hypertrophic scars and keloids (e.g., burns), and is preferably initiated after the proliferative phase has had time to progress (approximately 14 days after the initial injury), but before hypertrophic scar or keloid development. As noted above, the present invention also provides methods for treating neovascular diseases of the eye, including for example, corneal neovascularization, neovascular glaucoma, proliferative diabetic retinopathy, retrolental fibroplasia and macular degeneration.

[0579] Moreover, Ocular disorders associated with neovascularization which can be treated with the polynucleotides and polypeptides of the present invention (including agonists and/or antagonists) include, but are not limited to: neovascular glaucoma, diabetic retinopathy, retinoblastoma, retrolental fibroplasia, uveitis, retinopathy of prematurity macular degeneration, corneal graft neovascularization, as well as other eye inflammatory diseases, ocular tumors and diseases associated with choroidal or iris neovascularization. See, e.g., reviews by Waltman *et al., Am. J. Ophthal. 85*:704-710 (1978) and Gartner *et al., Surv. Ophthal. 22*:291-312 (1978).

[0580] Thus, within one aspect of the present invention methods are provided for treating neovascular diseases of the eye such as corneal neovascularization (including corneal graft neovascularization), comprising the step of administering to a patient a therapeutically effective amount of a compound (as described above) to the cornea, such that the formation of blood vessels is inhibited. Briefly, the cornea is a tissue which normally lacks blood vessels. In certain pathological conditions however, capillaries may extend into the cornea from the pericorneal vascular plexus of the limbus. When the cornea becomes vascularized, it also becomes clouded, resulting in a decline in the patient's visual acuity. Visual loss may become complete if the cornea completely opacitates. A wide variety of disorders can result in corneal neovascularization, including for example, corneal infections (e.g., trachoma, herpes simplex keratitis, leishmaniasis and onchocerciasis), immunological processes (e.g., graft rejection and Stevens-Johnson's syndrome), alkali burns, trauma, inflammation (of any cause), toxic and nutritional deficiency states, and as a complication of wearing contact lenses.

[0581] Within particularly preferred embodiments of the invention, may be prepared for topical administration in saline (combined with any of the preservatives and antimicrobial agents commonly used in ocular preparations), and administered in eyedrop form. The solution or suspension may be prepared in its pure form and administered several times daily. Alternatively, anti-angiogenic compositions, prepared as described above, may also be administered directly to the cornea. Within preferred embodiments, the anti-angiogenic composition is prepared with a muco-adhesive polymer which binds to cornea. Within further embodiments, the anti-angiogenic factors or anti-angiogenic compositions may be utilized as an adjunct to conventional steroid therapy. Topical therapy may also be useful prophylactically in corneal lesions which are known to have a

high probability of inducing an angiogenic response (such as chemical burns). In these instances the treatment, likely in combination with steroids, may be instituted immediately to help prevent subsequent complications.

[0582] Within other embodiments, the compounds described above may be injected directly into the corneal stroma by an ophthalmologist under microscopic guidance. The preferred site of injection may vary with the morphology of the individual lesion, but the goal of the administration would be to place the composition at the advancing front of the vasculature (i.e., interspersed between the blood vessels and the normal cornea). In most cases this would involve perilimbic corneal injection to "protect" the cornea from the advancing blood vessels. This method may also be utilized shortly after a corneal insult in order to prophylactically prevent corneal neovascularization. In this situation the material could be injected in the perilimbic cornea interspersed between the corneal lesion and its undesired potential limbic blood supply. Such methods may also be utilized in a similar fashion to prevent capillary invasion of transplanted corneas. In a sustained-release form injections might only be required 2-3 times per year. A steroid could also be added to the injection solution to reduce inflammation resulting from the injection itself.

[0583] Within another aspect of the present invention, methods are provided for treating neovascular glaucoma, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eye, such that the formation of blood vessels is inhibited. In one embodiment, the compound may be administered topically to the eye in order to treat early forms of neovascular glaucoma. Within other embodiments, the compound may be implanted by injection into the region of the anterior chamber angle. Within other embodiments, the compound may also be placed in any location such that the compound is continuously released into the aqueous humor. Within another aspect of the present invention, methods are provided for treating proliferative diabetic retinopathy, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eyes, such that the formation of blood vessels is inhibited.

[0584] Within particularly preferred embodiments of the invention, proliferative diabetic retinopathy may be treated by injection into the aqueous humor or the vitreous, in

order to increase the local concentration of the polynucleotide, polypeptide, antagonist and/or agonist in the retina. Preferably, this treatment should be initiated prior to the acquisition of severe disease requiring photocoagulation.

[0585] Within another aspect of the present invention, methods are provided for treating retrolental fibroplasia, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eye, such that the formation of blood vessels is inhibited. The compound may be administered topically, via intravitreous injection and/or via intraocular implants.

[0586] Additionally, disorders which can be treated with the polynucleotides, polypeptides, agonists and/or agonists include, but are not limited to, hemangioma, arthritis, psoriasis, angiofibroma, atherosclerotic plaques, delayed wound healing, granulations, hemophilic joints, hypertrophic scars, nonunion fractures, Osler-Weber syndrome, pyogenic granuloma, scleroderma, trachoma, and vascular adhesions.

[0587] Moreover, disorders and/or states, which can be treated with be treated with the the polynucleotides, polypeptides, agonists and/or agonists include, but are not limited to, solid tumors, blood born tumors such as leukemias, tumor metastasis, Kaposi's sarcoma, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas, rheumatoid arthritis, psoriasis, ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, and uvietis, delayed wound healing, endometriosis, vascluogenesis, granulations, hypertrophic scars (keloids), nonunion fractures, scleroderma, trachoma, vascular adhesions, myocardial angiogenesis, coronary collaterals, cerebral collaterals, arteriovenous malformations, ischemic limb angiogenesis, Osler-Webber Syndrome, plaque neovascularization, telangiectasia, hemophiliac joints, angiofibroma fibromuscular dysplasia, wound granulation, Crohn's disease, atherosclerosis, birth control agent by preventing vascularization required for embryo implantation controlling menstruation, diseases that have angiogenesis as a pathologic consequence such as cat scratch disease (Rochele minalia quintosa), ulcers (Helicobacter pylori), Bartonellosis and bacillary angiomatosis.

[0588] In one aspect of the birth control method, an amount of the compound sufficient to block embryo implantation is administered before or after intercourse and

fertilization have occurred, thus providing an effective method of birth control, possibly a "morning after" method. Polynucleotides, polypeptides, agonists and/or agonists may also be used in controlling menstruation or administered as either a peritoneal lavage fluid or for peritoneal implantation in the treatment of endometriosis.

[0589] Polynucleotides, polypeptides, agonists and/or agonists of the present invention may be incorporated into surgical sutures in order to prevent stitch granulomas.

[0590] Polynucleotides, polypeptides, agonists and/or agonists may be utilized in a wide variety of surgical procedures. For example, within one aspect of the present invention a compositions (in the form of, for example, a spray or film) may be utilized to coat or spray an area prior to removal of a tumor, in order to isolate normal surrounding tissues from malignant tissue, and/or to prevent the spread of disease to surrounding tissues. Within other aspects of the present invention, compositions (e.g., in the form of a spray) may be delivered via endoscopic procedures in order to coat tumors, or inhibit angiogenesis in a desired locale. Within yet other aspects of the present invention, surgical meshes which have been coated with anti- angiogenic compositions of the present invention may be utilized in any procedure wherein a surgical mesh might be utilized. For example, within one embodiment of the invention a surgical mesh laden with an anti-angiogenic composition may be utilized during abdominal cancer resection surgery (e.g., subsequent to colon resection) in order to provide support to the structure, and to release an amount of the anti-angiogenic factor.

[0591] Within further aspects of the present invention, methods are provided for treating tumor excision sites, comprising administering a polynucleotide, polypeptide, agonist and/or agonist to the resection margins of a tumor subsequent to excision, such that the local recurrence of cancer and the formation of new blood vessels at the site is inhibited. Within one embodiment of the invention, the anti-angiogenic compound is administered directly to the tumor excision site (e.g., applied by swabbing, brushing or otherwise coating the resection margins of the tumor with the anti-angiogenic compound). Alternatively, the anti-angiogenic compounds may be incorporated into known surgical pastes prior to administration. Within particularly preferred embodiments of the invention, the anti-angiogenic compounds are applied after hepatic resections for malignancy, and after neurosurgical operations.

[0592] Within one aspect of the present invention, polynucleotides, polypeptides, agonists and/or agonists may be administered to the resection margin of a wide variety of tumors, including for example, breast, colon, brain and hepatic tumors. For example, within one embodiment of the invention, anti-angiogenic compounds may be administered to the site of a neurological tumor subsequent to excision, such that the formation of new blood vessels at the site are inhibited.

[0593] The polynucleotides, polypeptides, agonists and/or agonists of the present invention may also be administered along with other anti-angiogenic factors. Representative examples of other anti-angiogenic factors include: Anti-Invasive Factor, retinoic acid and derivatives thereof, paclitaxel, Suramin, Tissue Inhibitor of Metalloproteinase-1, Tissue Inhibitor of Metalloproteinase-2, Plasminogen Activator Inhibitor-1, Plasminogen Activator Inhibitor-2, and various forms of the lighter "d group" transition metals.

[0594] Lighter "d group" transition metals include, for example, vanadium, molybdenum, tungsten, titanium, niobium, and tantalum species. Such transition metal species may form transition metal complexes. Suitable complexes of the above-mentioned transition metal species include oxo transition metal complexes.

[0595] Representative examples of vanadium complexes include oxo vanadium complexes such as vanadate and vanadyl complexes. Suitable vanadate complexes include metavanadate and orthovanadate complexes such as, for example, ammonium metavanadate, sodium metavanadate, and sodium orthovanadate. Suitable vanadyl complexes include, for example, vanadyl acetylacetonate and vanadyl sulfate including vanadyl sulfate hydrates such as vanadyl sulfate mono- and trihydrates.

[0596] Representative examples of tungsten and molybdenum complexes also include oxo complexes. Suitable oxo tungsten complexes include tungstate and tungsten oxide complexes. Suitable tungstate complexes include ammonium tungstate, calcium tungstate, sodium tungstate dihydrate, and tungstic acid. Suitable tungsten oxides include tungsten (IV) oxide and tungsten (VI) oxide. Suitable oxo molybdenum complexes include molybdate, molybdenum oxide, and molybdenyl complexes. Suitable molybdate complexes include ammonium molybdate and its hydrates, sodium molybdate and its hydrates, and potassium molybdate and its hydrates. Suitable molybdenum oxides include molybdenum (VI) oxide, molybdenum (VI) oxide, and molybdic acid. Suitable

molybdenyl complexes include, for example, molybdenyl acetylacetonate. Other suitable tungsten and molybdenum complexes include hydroxo derivatives derived from, for example, glycerol, tartaric acid, and sugars.

[0597] A wide variety of other anti-angiogenic factors may also be utilized within the context of the present invention. Representative examples include platelet factor 4; protamine sulphate; sulphated chitin derivatives (prepared from queen crab shells), (Murata et al., Cancer Res. 51:22-26, 1991); Sulphated Polysaccharide Peptidoglycan Complex (SP- PG) (the function of this compound may be enhanced by the presence of steroids such as estrogen, and tamoxifen citrate); Staurosporine; modulators of matrix metabolism, including for example, proline analogs, cishydroxyproline, d,L-3,4-dehydroproline, Thiaproline, alpha,alpha-dipyridyl, aminopropionitrile fumarate; 4-propyl-5-(4-pyridinyl)-2(3H)-oxazolone; Methotrexate; Mitoxantrone; Heparin; Interferons; 2 Macroglobulin-serum; ChIMP-3 (Pavloff et al., J. Bio. Chem. 267:17321-17326, 1992); Chymostatin (Tomkinson et al., Biochem J. 286:475-480, 1992); Cyclodextrin Tetradecasulfate; Eponemycin; Camptothecin; Fumagillin (Ingber et al., Nature 348:555-557, 1990); Gold Sodium Thiomalate ("GST"; Matsubara and Ziff, J. Clin. Invest. 79:1440-1446, 1987); anticollagenase-serum; alpha2-antiplasmin (Holmes et al., J. Biol. Chem. 262(4):1659-1664, 1987); Bisantrene (National Cancer Institute); Lobenzarit disodium (N-(2)-carboxyphenyl-4- chloroanthronilic acid disodium or "CCA"; Takeuchi et al., Agents Actions 36:312-316, 1992); Thalidomide; Angostatic steroid; AGM-1470; carboxynaminolmidazole; and metalloproteinase inhibitors such as BB94.

Musculoskeletal System Disorders

[0598] Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention, may be used to treat, prevent, diagnose, and/or prognose disorders of the musculoskeletal system, including but not limited to, disorders of the bone, joints, ligaments, tendons, bursa, muscle, and/or neoplasms and cancers associated with musculoskeletal tissue.

[0599] Diseases or disorders of the bone include, but are not limited to, Albers-Schönberg disease, bowlegs, heel spurs, Köhler's bone disease, knock-knees, Legg-Calvé-Perthes disease, Marfan's syndrome, mucopolysaccharidoses, Osgood-Schlatter disease, osteochondroses, osteochondrodysplasia, osteomyelitis, osteopetroses, osteoporosis

(postmenopausal, senile, and juvenile), Paget's disease, Scheuermann's disease, scoliosis, Sever's disease, and patellofemoral stress syndrome.

[0600] Joint diseases or disorders include, but are not limited to, ankylosing spondylitis, Behçet's syndrome, CREST syndrome, Ehlers-Danlos syndrome, infectious arthritis, discoid lupus erythematosus, systemic lupus erythematosus, Lyme disease, osteoarthritis, psoriatic arthritis, relapsing polychondrites, Reiter's syndrome, rheumatoid arthritis (adult and juvenile), scleroderma, and Still's disease.

[0601] Diseases or disorders affecting ligaments, tendons, or bursa include, but are not limited to, ankle sprain, bursitis, posterior Achilles tendon bursitis (Haglund's deformity), anterior Achilles tendon bursitis (Albert's disease), tendinitis, tenosynovitis, poplieus tendinitis, Achilles tendinitis, medial or lateral epicondylitis, rotator cuff tendinitis, spasmodic torticollis, and fibromyalgia syndrome.

[0602] Muscle diseases or disorders include, but are not limited to, Becker's muscular dystrophy, Duchenne's muscular dystrophy, Landouzy-Dejerine muscular dystrophy, Leyden-Möbius muscular dystrophy, Erb's muscular dystrophy, Charcot's joints, dermatomyositis, gout, pseudogout, glycogen storage diseases, Pompe's disease, mitochondrial myopathy, periodic paralysis, polymyalgia rheumatica, polymyositis, Steinert's disease, Thomsen's disease, anterolateral and posteromedial shin splints, posterior femoral muscle strain, and fibromyositis.

[0603] Musculoskeletal tissue may also develop cancers and/or neoplasms that include, but are not limited to, osteochondroma, benign chondroma, chondroblastoma, chondromyxoid fibroma, osteoid osteoma, giant cell tumor, multiple myeloma, osteosarcoma, fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's tumor, and malignant lymphoma of bone.

Neural Activity and Neurological Diseases

[0604] The polynucleotides, polypeptides and agonists or antagonists of the invention may be used for the diagnosis and/or treatment of diseases, disorders, damage or injury of the brain and/or nervous system. Nervous system disorders that can be treated with the compositions of the invention (e.g., polypeptides, polynucleotides, and/or agonists or antagonists), include, but are not limited to, nervous system injuries, and diseases or disorders which result in either a disconnection of axons, a diminution or

degeneration of neurons, or demyelination. Nervous system lesions which may be treated in a patient (including human and non-human mammalian patients) according to the methods of the invention, include but are not limited to, the following lesions of either the central (including spinal cord, brain) or peripheral nervous systems: (1) ischemic lesions, in which a lack of oxygen in a portion of the nervous system results in neuronal injury or death, including cerebral infarction or ischemia, or spinal cord infarction or ischemia; (2) traumatic lesions, including lesions caused by physical injury or associated with surgery, for example, lesions which sever a portion of the nervous system, or compression injuries; (3) malignant lesions, in which a portion of the nervous system is destroyed or injured by malignant tissue which is either a nervous system associated malignancy or a malignancy derived from non-nervous system tissue; (4) infectious lesions, in which a portion of the nervous system is destroyed or injured as a result of infection, for example, by an abscess or associated with infection by human immunodeficiency virus, herpes zoster, or herpes simplex virus or with Lyme disease, tuberculosis, or syphilis; (5) degenerative lesions, in which a portion of the nervous system is destroyed or injured as a result of a degenerative process including but not limited to, degeneration associated with Parkinson's disease, Alzheimer's disease, Huntington's chorea, or amyotrophic lateral sclerosis (ALS); (6) lesions associated with nutritional diseases or disorders, in which a portion of the nervous system is destroyed or injured by a nutritional disorder or disorder of metabolism including, but not limited to, vitamin B12 deficiency, folic acid deficiency, Wernicke disease, tobacco-alcohol amblyopia, Marchiafava-Bignami disease (primary degeneration of the corpus callosum), and alcoholic cerebellar degeneration; (7) neurological lesions associated with systemic diseases including, but not limited to, diabetes (diabetic neuropathy, Bell's palsy), systemic lupus erythematosus, carcinoma, or sarcoidosis; (8) lesions caused by toxic substances including alcohol, lead, or particular neurotoxins; and (9) demyelinated lesions in which a portion of the nervous system is destroyed or injured by a demyelinating disease including, but not limited to, multiple sclerosis, human immunodeficiency virus-associated myelopathy, transverse myelopathy or various etiologies, progressive multifocal leukoencephalopathy, and central pontine myelinolysis.

[0605] In one embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to protect neural cells from the damaging effects of hypoxia. In a further preferred embodiment, the polypeptides, polynucleotides, or agonists

or antagonists of the invention are used to protect neural cells from the damaging effects of cerebral hypoxia. According to this embodiment, the compositions of the invention are used to treat or prevent neural cell injury associated with cerebral hypoxia. In one non-exclusive aspect of this embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention, are used to treat or prevent neural cell injury associated with cerebral ischemia. In another non-exclusive aspect of this embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent neural cell injury associated with cerebral infarction.

[0606] In another preferred embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent neural cell injury associated with a stroke. In a specific embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent cerebral neural cell injury associated with a stroke.

[0607] In another preferred embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent neural cell injury associated with a heart attack. In a specific embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat or prevent cerebral neural cell injury associated with a heart attack.

[0608] The compositions of the invention which are useful for treating or preventing a nervous system disorder may be selected by testing for biological activity in promoting the survival or differentiation of neurons. For example, and not by way of limitation, compositions of the invention which elicit any of the following effects may be useful according to the invention: (1) increased survival time of neurons in culture either in the presence or absence of hypoxia or hypoxic conditions; (2) increased sprouting of neurons in culture or *in vivo*; (3) increased production of a neuron-associated molecule in culture or *in vivo*, *e.g.*, choline acetyltransferase or acetylcholinesterase with respect to motor neurons; or (4) decreased symptoms of neuron dysfunction *in vivo*. Such effects may be measured by any method known in the art. In preferred, non-limiting embodiments, increased survival of neurons may routinely be measured using a method set forth herein or otherwise known in the art, such as, for example, in Zhang *et al.*, *Proc Natl Acad Sci USA* 97:3637-42 (2000) or in Arakawa *et al.*, *J. Neurosci.*, *10*:3507-15 (1990); increased sprouting of neurons may be detected by methods known in the art, such

as, for example, the methods set forth in Pestronk *et al., Exp. Neurol., 70*:65-82 (1980), or Brown *et al., Ann. Rev. Neurosci., 4*:17-42 (1981); increased production of neuron-associated molecules may be measured by bioassay, enzymatic assay, antibody binding, Northern blot assay, etc., using techniques known in the art and depending on the molecule to be measured; and motor neuron dysfunction may be measured by assessing the physical manifestation of motor neuron disorder, e.g., weakness, motor neuron conduction velocity, or functional disability.

[0609] In specific embodiments, motor neuron disorders that may be treated according to the invention include, but are not limited to, disorders such as infarction, infection, exposure to toxin, trauma, surgical damage, degenerative disease or malignancy that may affect motor neurons as well as other components of the nervous system, as well as disorders that selectively affect neurons such as amyotrophic lateral sclerosis, and including, but not limited to, progressive spinal muscular atrophy, progressive bulbar palsy, primary lateral sclerosis, infantile and juvenile muscular atrophy, progressive bulbar paralysis of childhood (Fazio-Londe syndrome), poliomyelitis and the post polio syndrome, and Hereditary Motorsensory Neuropathy (Charcot-Marie-Tooth Disease).

[0610] Further, polypeptides or polynucleotides of the invention may play a role in neuronal survival; synapse formation; conductance; neural differentiation, etc. Thus, compositions of the invention (including polynucleotides, polypeptides, and agonists or antagonists) may be used to diagnose and/or treat or prevent diseases or disorders associated with these roles, including, but not limited to, learning and/or cognition disorders. The compositions of the invention may also be useful in the treatment or prevention of neurodegenerative disease states and/or behavioural disorders. Such neurodegenerative disease states and/or behavioral disorders include, but are not limited to, Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, compositions of the invention may also play a role in the treatment, prevention and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders.

[0611] Additionally, polypeptides, polynucleotides and/or agonists or antagonists of the invention, may be useful in protecting neural cells from diseases, damage, disorders,

or injury, associated with cerebrovascular disorders including, but not limited to, carotid artery diseases (e.g., carotid artery thrombosis, carotid stenosis, or Moyamoya Disease), cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformations, cerebral artery diseases, cerebral embolism and thrombosis (e.g., carotid artery thrombosis, sinus thrombosis, or Wallenberg's Syndrome), cerebral hemorrhage (e.g., epidural or subdural hematoma, or subarachnoid hemorrhage), cerebral infarction, cerebral ischemia (e.g., transient cerebral ischemia, Subclavian Steal Syndrome, or vertebrobasilar insufficiency), vascular dementia (e.g., multi-infarct), leukomalacia, periventricular, and vascular headache (e.g., cluster headache or migraines).

[0612] In accordance with yet a further aspect of the present invention, there is provided a process for utilizing polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, for therapeutic purposes, for example, to stimulate neurological cell proliferation and/or differentiation. Therefore, polynucleotides, polypeptides, agonists and/or antagonists of the invention may be used to treat and/or detect neurologic diseases. Moreover, polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used as a marker or detector of a particular nervous system disease or disorder.

[0613] Examples of neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include brain diseases, such as metabolic brain diseases which includes phenylketonuria such as maternal phenylketonuria, pyruvate carboxylase deficiency, pyruvate dehydrogenase complex deficiency, Wernicke's Encephalopathy, brain edema, brain neoplasms such as cerebellar neoplasms which include infratentorial neoplasms, cerebral ventricle neoplasms such as choroid plexus neoplasms, hypothalamic neoplasms, supratentorial neoplasms, canavan disease, cerebellar diseases such as cerebellar ataxia which include spinocerebellar degeneration such as ataxia telangiectasia, cerebellar dyssynergia, Friederich's Ataxia, Machado-Joseph Disease, olivopontocerebellar atrophy, cerebellar neoplasms such as infratentorial neoplasms, diffuse cerebral sclerosis such as encephalitis periaxialis, globoid cell leukodystrophy, metachromatic leukodystrophy and subacute sclerosing panencephalitis.

[0614] Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention

include cerebrovascular disorders (such as carotid artery diseases which include carotid artery thrombosis, carotid stenosis and Moyamoya Disease), cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformations, cerebral artery diseases, cerebral embolism and thrombosis such as carotid artery thrombosis, sinus thrombosis and Wallenberg's Syndrome, cerebral hemorrhage such as epidural hematoma, subdural hematoma and subarachnoid hemorrhage, cerebral infarction, cerebral ischemia such as transient cerebral ischemia, Subclavian Steal Syndrome and vertebrobasilar insufficiency, vascular dementia such as multi-infarct dementia, periventricular leukomalacia, vascular headache such as cluster headache and migraine.

[0615] Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include dementia such as AIDS Dementia Complex, presenile dementia such as Alzheimer's Disease and Creutzfeldt-Jakob Syndrome, senile dementia such as Alzheimer's Disease and progressive supranuclear palsy, vascular dementia such as multi-infarct dementia, encephalitis which include encephalitis periaxialis, viral encephalitis such as epidemic encephalitis, Japanese Encephalitis, St. Louis Encephalitis, tick-borne encephalitis and West Nile Fever, acute disseminated encephalomyelitis, meningoencephalitis such as uveomeningoencephalitic syndrome, Postencephalitic Parkinson Disease and subacute sclerosing panencephalitis, encephalomalacia such as periventricular leukomalacia, epilepsy such as generalized epilepsy which includes infantile spasms, absence epilepsy, myoclonic epilepsy which includes MERRF Syndrome, tonic-clonic epilepsy, partial epilepsy such as complex partial epilepsy, frontal lobe epilepsy and temporal lobe epilepsy, post-traumatic epilepsy, status epilepticus such as Epilepsia Partialis Continua, and Hallervorden-Spatz Syndrome.

[0616] Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include hydrocephalus such as Dandy-Walker Syndrome and normal pressure hydrocephalus, hypothalamic diseases such as hypothalamic neoplasms, cerebral malaria, narcolepsy which includes cataplexy, bulbar poliomyelitis, cerebri pseudotumor, Rett Syndrome, Reye's Syndrome, thalamic diseases, cerebral toxoplasmosis, intracranial tuberculoma and Zellweger Syndrome, central nervous system infections such as AIDS

Dementia Complex, Brain Abscess, subdural empyema, encephalomyelitis such as Equine Encephalomyelitis, Venezuelan Equine Encephalomyelitis, Necrotizing Hemorrhagic Encephalomyelitis, Visna, and cerebral malaria.

[0617] Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include meningitis such as arachnoiditis, aseptic meningtitis such as viral meningtitis which includes lymphocytic choriomeningitis, Bacterial meningtitis which includes Haemophilus Meningtitis, Listeria Meningtitis, Meningococcal Meningtitis such as Waterhouse-Friderichsen Syndrome, Pneumococcal Meningtitis and meningeal tuberculosis, fungal meningitis such as Cryptococcal Meningtitis, subdural effusion, meningoencephalitis such as uvemeningoencephalitic syndrome, myelitis such as transverse myelitis, neurosyphilis such as tabes dorsalis, poliomyelitis which includes bulbar poliomyelitis and postpoliomyelitis syndrome, prion diseases (such as Creutzfeldt-Jakob Syndrome, Bovine Spongiform Encephalopathy, Gerstmann-Straussler Syndrome, Kuru, Scrapie), and cerebral toxoplasmosis.

[0618] Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include central nervous system neoplasms such as brain neoplasms that include cerebellar neoplasms such as infratentorial neoplasms, cerebral ventricle neoplasms such as choroid plexus neoplasms, hypothalamic neoplasms and supratentorial neoplasms, meningeal neoplasms, spinal cord neoplasms which include epidural neoplasms, demyelinating diseases such as Canavan Diseases, diffuse cerebral sceloris which includes adrenoleukodystrophy, encephalitis periaxialis, globoid cell leukodystrophy, diffuse cerebral sclerosis such as metachromatic leukodystrophy, allergic encephalomyelitis, necrotizing hemorrhagic encephalomyelitis, progressive multifocal leukoencephalopathy, multiple sclerosis, central pontine myelinolysis, transverse myelitis, neuromyelitis optica, Scrapie, Swayback, Chronic Fatigue Syndrome, Visna, High Pressure Nervous Syndrome, Meningism, spinal cord diseases such as amyotonia congenita, amyotrophic lateral sclerosis, spinal muscular atrophy such as Werdnig-Hoffmann Disease, spinal cord compression, spinal cord neoplasms such as epidural neoplasms, syringomyelia, Tabes Dorsalis, Stiff-Man Syndrome, mental retardation such as Angelman Syndrome, Cri-du-Chat Syndrome, De Lange's Syndrome, Down Syndrome, Gangliosidoses such as

gangliosidoses G(M1), Sandhoff Disease, Tay-Sachs Disease, Hartnup Disease, homocystinuria, Laurence-Moon- Biedl Syndrome, Lesch-Nyhan Syndrome, Maple Syrup Urine Disease, mucolipidosis such as fucosidosis, neuronal ceroid-lipofuscinosis, oculocerebrorenal syndrome, phenylketonuria such as maternal phenylketonuria, Prader-Willi Syndrome, Rett Syndrome, Rubinstein-Taybi Syndrome, Tuberous Sclerosis, WAGR Syndrome, nervous system abnormalities such as holoprosencephaly, neural tube defects such as anencephaly which includes hydrangencephaly, Arnold-Chairi Deformity, encephalocele, meningocele, meningomyelocele, spinal dysraphism such as spina bifida cystica and spina bifida occulta.

[0619] Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include hereditary motor and sensory neuropathies which include Charcot-Marie Disease, Hereditary optic atrophy, Refsum's Disease, hereditary spastic paraplegia, Werdnig-Hoffmann Disease, Hereditary Sensory and Autonomic Neuropathies such as Congenital Analgesia and Familial Dysautonomia, Neurologic manifestations (such as agnosia that include Gerstmann's Syndrome, Amnesia such as retrograde amnesia, apraxia, neurogenic bladder, cataplexy, communicative disorders such as hearing disorders that includes deafness, partial hearing loss, loudness recruitment and tinnitus, language disorders such as aphasia which include agraphia, anomia, broca aphasia, and Wernicke Aphasia, Dyslexia such as Acquired Dyslexia, language development disorders, speech disorders such as aphasia which includes anomia, broca aphasia and Wernicke Aphasia, articulation disorders, communicative disorders such as speech disorders which include dysarthria, echolalia, mutism and stuttering, voice disorders such as aphonia and hoarseness, decerebrate state, delirium, fasciculation, hallucinations, meningism, movement disorders such as angelman syndrome, ataxia, athetosis, chorea, dystonia, hypokinesia, muscle hypotonia, myoclonus, tic, torticollis and tremor, muscle hypertonia such as muscle rigidity such as stiff-man syndrome, muscle spasticity, paralysis such as facial paralysis which includes Herpes Zoster Oticus, Gastroparesis, Hemiplegia, ophthalmoplegia such as diplopia, Duane's Syndrome, Horner's Syndrome, Chronic progressive external ophthalmoplegia such as Kearns Syndrome, Bulbar Paralysis, Tropical Spastic Paraparesis, Paraplegia such as Brown-Sequard Syndrome, quadriplegia, respiratory paralysis and vocal cord paralysis, paresis, phantom limb, taste disorders such as ageusia

and dysgeusia, vision disorders such as amblyopia, blindness, color vision defects, diplopia, hemianopsia, scotoma and subnormal vision, sleep disorders such as hypersomnia which includes Kleine-Levin Syndrome, insomnia, and somnambulism, spasm such as trismus, unconsciousness such as coma, persistent vegetative state and syncope and vertigo, neuromuscular diseases such as amyotonia congenita, amyotrophic lateral sclerosis, Lambert-Eaton Myasthenic Syndrome, motor neuron disease, muscular atrophy such as spinal muscular atrophy, Charcot-Marie Disease and Werdnig-Hoffmann Disease, Postpoliomyelitis Syndrome, Muscular Dystrophy, Myasthenia Gravis, Myotonia Atrophica, Myotonia Confenita, Nemaline Myopathy, Familial Periodic Paralysis, Multiplex Paramyloclonus, Tropical Spastic Paraparesis and Stiff-Man Syndrome, peripheral nervous system diseases such as acrodynia, amyloid neuropathies, autonomic nervous system diseases such as Adie's Syndrome, Barre-Lieou Syndrome, Familial Dysautonomia, Horner's Syndrome, Reflex Sympathetic Dystrophy and Shy-Drager Syndrome, Cranial Nerve Diseases such as Acoustic Nerve Diseases such as Acoustic Neuroma which includes Neurofibromatosis 2, Facial Nerve Diseases such as Facial Neuralgia,Melkersson-Rosenthal Syndrome, ocular motility disorders which includes amblyopia, nystagmus, oculomotor nerve paralysis, ophthalmoplegia such as Duane's Syndrome, Horner's Syndrome, Chronic Progressive External Ophthalmoplegia which includes Kearns Syndrome, Strabismus such as Esotropia and Exotropia, Oculomotor Nerve Paralysis, Optic Nerve Diseases such as Optic Atrophy which includes Hereditary Optic Atrophy, Optic Disk Drusen, Optic Neuritis such as Neuromyelitis Optica, Papilledema, Trigeminal Neuralgia, Vocal Cord Paralysis, Demyelinating Diseases such as Neuromyelitis Optica and Swayback, and Diabetic neuropathies such as diabetic foot.

[0620] Additional neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include nerve compression syndromes such as carpal tunnel syndrome, tarsal tunnel syndrome, thoracic outlet syndrome such as cervical rib syndrome, ulnar nerve compression syndrome, neuralgia such as causalgia, cervico-brachial neuralgia, facial neuralgia and trigeminal neuralgia, neuritis such as experimental allergic neuritis, optic neuritis, polyneuritis, polyradiculoneuritis and radiculities such as polyradiculitis, hereditary motor and sensory neuropathies such as Charcot-Marie Disease, Hereditary Optic Atrophy, Refsum's Disease, Hereditary Spastic Paraplegia and Werdnig-Hoffmann

Disease, Hereditary Sensory and Autonomic Neuropathies which include Congenital Analgesia and Familial Dysautonomia, POEMS Syndrome, Sciatica, Gustatory Sweating and Tetany).

Endocrine Disorders

[0621] Polynucleotides or polypeptides, or agonists or antagonists of the present invention, may be used to treat, prevent, diagnose, and/or prognose disorders and/or diseases related to hormone imbalance, and/or disorders or diseases of the endocrine system.

[0622] Hormones secreted by the glands of the endocrine system control physical growth, sexual function, metabolism, and other functions. Disorders may be classified in two ways: disturbances in the production of hormones, and the inability of tissues to respond to hormones. The etiology of these hormone imbalance or endocrine system diseases, disorders or conditions may be genetic, somatic, such as cancer and some autoimmune diseases, acquired (e.g., by chemotherapy, injury or toxins), or infectious. Moreover, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention can be used as a marker or detector of a particular disease or disorder related to the endocrine system and/or hormone imbalance.

[0623] Endocrine system and/or hormone imbalance and/or diseases encompass disorders of uterine motility including, but not limited to: complications with pregnancy and labor (e.g., pre-term labor, post-term pregnancy, spontaneous abortion, and slow or stopped labor); and disorders and/or diseases of the menstrual cycle (e.g., dysmenorrhea and endometriosis).

[0624] Endocrine system and/or hormone imbalance disorders and/or diseases include disorders and/or diseases of the pancreas, such as, for example, diabetes mellitus, diabetes insipidus, congenital pancreatic agenesis, pheochromocytoma--islet cell tumor syndrome; disorders and/or diseases of the adrenal glands such as, for example, Addison's Disease, corticosteroid deficiency, virilizing disease, hirsutism, Cushing's Syndrome, hyperaldosteronism, pheochromocytoma; disorders and/or diseases of the pituitary gland, such as, for example, hyperpituitarism, hypopituitarism, pituitary dwarfism, pituitary adenoma, panhypopituitarism, acromegaly, gigantism; disorders and/or diseases of the thyroid, including but not limited to, hyperthyroidism, hypothyroidism, Plummer's

disease, Graves' disease (toxic diffuse goiter), toxic nodular goiter, thyroiditis (Hashimoto's thyroiditis, subacute granulomatous thyroiditis, and silent lymphocytic thyroiditis), Pendred's syndrome, myxedema, cretinism, thyrotoxicosis, thyroid hormone coupling defect, thymic aplasia, Hurthle cell tumours of the thyroid, thyroid cancer, thyroid carcinoma, Medullary thyroid carcinoma; disorders and/or diseases of the parathyroid, such as, for example, hyperparathyroidism, hypoparathyroidism; disorders and/or diseases of the hypothalamus.

[0625] In addition, endocrine system and/or hormone imbalance disorders and/or diseases may also include disorders and/or diseases of the testes or ovaries, including cancer. Other disorders and/or diseases of the testes or ovaries further include, for example, ovarian cancer, polycystic ovary syndrome, Klinefelter's syndrome, vanishing testes syndrome (bilateral anorchia), congenital absence of Leydig's cells, cryptorchidism, Noonan's syndrome, myotonic dystrophy, capillary haemangioma of the testis (benign), neoplasias of the testis and neo-testis.

[0626] Moreover, endocrine system and/or hormone imbalance disorders and/or diseases may also include disorders and/or diseases such as, for example, polyglandular deficiency syndromes, pheochromocytoma, neuroblastoma, multiple Endocrine neoplasia, and disorders and/or cancers of endocrine tissues.

Gastrointestinal Disorders

[0627] Polynucleotides or polypeptides, or agonists or antagonists of the present invention, may be used to treat, prevent, diagnose, and/or prognose gastrointestinal disorders, including inflammatory diseases and/or conditions, infections, cancers (e.g., intestinal neoplasms (carcinoid tumor of the small intestine, non-Hodgkin's lymphoma of the small intestine, small bowl lymphoma)), and ulcers, such as peptic ulcers.

[0628] Gastrointestinal disorders include dysphagia, odynophagia, inflammation of the esophagus, peptic esophagitis, gastric reflux, submucosal fibrosis and stricturing, Mallory-Weiss lesions, leiomyomas, lipomas, epidermal cancers, adeoncarcinomas, gastric retention disorders, gastroenteritis, gastric atrophy, gastric/stomach cancers, polyps of the stomach, autoimmune disorders such as pernicious anemia, pyloric stenosis, gastritis (bacterial, viral, eosinophilic, stress-induced, chronic erosive, atrophic, plasma cell, and Ménétrier's), and peritoneal diseases (e.g., chyloperioneum, hemoperitoneum,

mesenteric cyst, mesenteric lymphadenitis, mesenteric vascular occlusion, panniculitis, neoplasms, peritonitis, pneumoperitoneum, bubphrenic abscess).

[0629] Gastrointestinal disorders also include disorders associated with the small intestine, such as malabsorption syndromes, distension, irritable bowel syndrome, sugar intolerance, celiac disease, duodenal ulcers, duodenitis, tropical sprue, Whipple's disease, intestinal lymphangiectasia, Crohn's disease, appendicitis, obstructions of the ileum, Meckel's diverticulum, multiple diverticula, failure of complete rotation of the small and large intestine, lymphoma, and bacterial and parasitic diseases (such as Traveler's diarrhea, typhoid and paratyphoid, cholera, infection by Roundworms (*Ascariasis lumbricoides*), Hookworms (*Ancylostoma duodenale*), Threadworms (*Enterobius vermicularis*), Tapeworms (*Taenia saginata*, *Echinococcus granulosus*, *Diphyllobothrium spp.*, and *T. solium*).

[0630] Liver diseases and/or disorders include intrahepatic cholestasis (alagille syndrome, biliary liver cirrhosis), fatty liver (alcoholic fatty liver, reye syndrome), hepatic vein thrombosis, hepatolentricular degeneration, hepatomegaly, hepatopulmonary syndrome, hepatorenal syndrome, portal hypertension (esophageal and gastric varices), liver abscess (amebic liver abscess), liver cirrhosis (alcoholic, biliary and experimental), alcoholic liver diseases (fatty liver, hepatitis, cirrhosis), parasitic (hepatic echinococcosis, fascioliasis, amebic liver abscess), jaundice (hemolytic, hepatocellular, and cholestatic), cholestasis, portal hypertension, liver enlargement, ascites, hepatitis (alcoholic hepatitis, animal hepatitis, chronic hepatitis (autoimmune, hepatitis B, hepatitis C, hepatitis D, drug induced), toxic hepatitis, viral human hepatitis (hepatitis A, hepatitis B, hepatitis C, hepatitis D, hepatitis E), Wilson's disease, granulomatous hepatitis, secondary biliary cirrhosis, hepatic encephalopathy, portal hypertension, varices, hepatic encephalopathy, primary biliary cirrhosis, primary sclerosing cholangitis, hepatocellular adenoma, hemangiomas, bile stones, liver failure (hepatic encephalopathy, acute liver failure), and liver neoplasms (angiomyolipoma, calcified liver metastases, cystic liver metastases, epithelial tumors, fibrolamellar hepatocarcinoma, focal nodular hyperplasia, hepatic adenoma, hepatobiliary cystadenoma, hepatoblastoma, hepatocellular carcinoma, hepatoma, liver cancer, liver hemangioendothelioma, mesenchymal hamartoma, mesenchymal tumors of liver, nodular regenerative hyperplasia, benign liver tumors (Hepatic cysts [Simple cysts, Polycystic liver disease, Hepatobiliary cystadenoma,

Choledochal cyst], Mesenchymal tumors [Mesenchymal hamartoma, Infantile hemangioendothelioma, Hemangioma, Peliosis hepatis, Lipomas, Inflammatory pseudotumor, Miscellaneous], Epithelial tumors [Bile duct epithelium (Bile duct hamartoma, Bile duct adenoma), Hepatocyte (Adenoma, Focal nodular hyperplasia, Nodular regenerative hyperplasia)], malignant liver tumors [hepatocellular, hepatoblastoma, hepatocellular carcinoma, cholangiocellular, cholangiocarcinoma, cystadenocarcinoma, tumors of blood vessels, angiosarcoma, Karposi's sarcoma, hemangioendothelioma, other tumors, embryonal sarcoma, fibrosarcoma, leiomyosarcoma, rhabdomyosarcoma, carcinosarcoma, teratoma, carcinoid, squamous carcinoma, primary lymphoma]), peliosis hepatis, erythrohepatic porphyria, hepatic porphyria (acute intermittent porphyria, porphyria cutanea tarda), Zellweger syndrome).

[0631] Pancreatic diseases and/or disorders include acute pancreatitis, chronic pancreatitis (acute necrotizing pancreatitis, alcoholic pancreatitis), neoplasms (adenocarcinoma of the pancreas, cystadenocarcinoma, insulinoma, gastrinoma, and glucagonoma, cystic neoplasms, islet-cell tumors, pancreoblastoma), and other pancreatic diseases (e.g., cystic fibrosis, cyst (pancreatic pseudocyst, pancreatic fistula, insufficiency)).

[0632] Gallbladder diseases include gallstones (cholelithiasis and choledocholithiasis), postcholecystectomy syndrome, diverticulosis of the gallbladder, acute cholecystitis, chronic cholecystitis, bile duct tumors, and mucocele.

[0633] Diseases and/or disorders of the large intestine include antibiotic-associated colitis, diverticulitis, ulcerative colitis, acquired megacolon, abscesses, fungal and bacterial infections, anorectal disorders (e.g., fissures, hemorrhoids), colonic diseases (colitis, colonic neoplasms [colon cancer, adenomatous colon polyps (e.g., villous adenoma), colon carcinoma, colorectal cancer], colonic diverticulitis, colonic diverticulosis, megacolon [Hirschsprung disease, toxic megacolon]; sigmoid diseases [proctocolitis, sigmoin neoplasms]), constipation, Crohn's disease, diarrhea (infantile diarrhea, dysentery), duodenal diseases (duodenal neoplasms, duodenal obstruction, duodenal ulcer, duodenitis), enteritis (enterocolitis), HIV enteropathy, ileal diseases (ileal neoplasms, ileitis), immunoproliferative small intestinal disease, inflammatory bowel disease (ulcerative colitis, Crohn's disease), intestinal atresia, parasitic diseases (anisakiasis, balantidiasis, blastocystis infections, cryptosporidiosis, dientamoebiasis,

amebic dysentery, giardiasis), intestinal fistula (rectal fistula), intestinal neoplasms (cecal neoplasms, colonic neoplasms, duodenal neoplasms, ileal neoplasms, intestinal polyps, jejunal neoplasms, rectal neoplasms), intestinal obstruction (afferent loop syndrome, duodenal obstruction, impacted feces, intestinal pseudo-obstruction [cecal volvulus], intussusception), intestinal perforation, intestinal polyps (colonic polyps, gardner syndrome, peutz-jeghers syndrome), jejunal diseases (jejunal neoplasms), malabsorption syndromes (blind loop syndrome, celiac disease, lactose intolerance, short bowl syndrome, tropical sprue, whipple's disease), mesenteric vascular occlusion, pneumatosis cystoides intestinalis, protein-losing enteropathies (intestinal lymphagiectasis), rectal diseases (anus diseases, fecal incontinence, hemorrhoids, proctitis, rectal fistula, rectal prolapse, rectocele), peptic ulcer (duodenal ulcer, peptic esophagitis, hemorrhage, perforation, stomach ulcer, Zollinger-Ellison syndrome), postgastrectomy syndromes (dumping syndrome), stomach diseases (e.g., achlorhydria, duodenogastric reflux (bile reflux), gastric antral vascular ectasia, gastric fistula, gastric outlet obstruction, gastritis (atrophic or hypertrophic), gastroparesis, stomach dilatation, stomach diverticulum, stomach neoplasms (gastric cancer, gastric polyps, gastric adenocarcinoma, hyperplastic gastric polyp), stomach rupture, stomach ulcer, stomach volvulus), tuberculosis, visceroptosis, vomiting (e.g., hematemesis, hyperemesis gravidarum, postoperative nausea and vomiting) and hemorrhagic colitis.

[0634] Further diseases and/or disorders of the gastrointestinal system include biliary tract diseases, such as, gastroschisis, fistula (e.g., biliary fistula, esophageal fistula, gastric fistula, intestinal fistula, pancreatic fistula), neoplasms (e.g., biliary tract neoplasms, esophageal neoplasms, such as adenocarcinoma of the esophagus, esophageal squamous cell carcinoma, gastrointestinal neoplasms, pancreatic neoplasms, such as adenocarcinoma of the pancreas, mucinous cystic neoplasm of the pancreas, pancreatic cystic neoplasms, pancreatoblastoma, and peritoneal neoplasms), esophageal disease (e.g., bullous diseases, candidiasis, glycogenic acanthosis, ulceration, barrett esophagus varices, atresia, cyst, diverticulum (e.g., Zenker's diverticulum), fistula (e.g., tracheoesophageal fistula), motility disorders (e.g., CREST syndrome, deglutition disorders, achalasia, spasm, gastroesophageal reflux), neoplasms, perforation (e.g., Boerhaave syndrome, Mallory-Weiss syndrome), stenosis, esophagitis, diaphragmatic hernia (e.g., hiatal hernia); gastrointestinal diseases, such as, gastroenteritis (e.g., cholera morbus, norwalk virus

infection), hemorrhage (e.g., hematemesis, melena, peptic ulcer hemorrhage), stomach neoplasms (gastric cancer, gastric polyps, gastric adenocarcinoma, stomach cancer)), hernia (e.g., congenital diaphragmatic hernia, femoral hernia, inguinal hernia, obturator hernia, umbilical hernia, ventral hernia), and intestinal diseases (e.g., cecal diseases (appendicitis, cecal neoplasms)).

Developmental and Inherited Disorders

[0635] Polynuceotides or polypeptides, or agonists or antagonists of the present invention may be used to treat, prevent, diagnose, and/or prognose diseases associated with mixed fetal tissues, including, but not limited to, developmental and inherited disorders or defects of the nervous system, musculoskelelal system, execretory system, cardiovascular system, hematopoietic system, gastrointestinal system, reproductive system, and respiratory system. Compositions of the present invention may also be used to treat, prevent, diagnose, and/or prognose developmental and inherited disorders or defects associated with, but not limited to, skin, hair, visual, and auditory tissues, metabolism. Additionally, the compositions of the invention may be useful in the diagnosis, treatment, and/or prevention of disorders or diseases associated with, but not limited to, chromosomal or genetic abnormalities and hyperproliferation or neoplasia.

[0636] Disorders or defects of the nervous system associated with developmental or inherited abnormalities that may be diagnosed, treated, and/or prevented with the compostions of the invention include, but are not limited to, adrenoleukodystrophy, agenesis of corpus callosum, Alexander disease, anencephaly, Angelman syndrome, Arnold-Chiari deformity, Batten disease, Canavan disease, cephalic disorders, Charcot-Marie-Tooth disease, encephalocele, Friedreich's ataxia, Gaucher's disease, Gorlin syndrome, Hallervorden-Spatz disease, hereditary spastic paraplegia, Huntington disease, hydranencephaly, hydrocephalus, Joubert syndrome, Lesch-Nyhan syndrome, leukodystrophy, Menkes disease, microcephaly, Niemann-Pick Type C1, neurofibromatosis, porencephaly, progeria, proteus syndrome, Refsum disease, spina bifida, Sturge-Weber syndrome, Tay-Sachs disease, tuberous sclerosis, and von Hippel-Lindau disease.

[0637] Developmental and inherited disorders resulting in disorders or defects of the musculoskeletal system that may be diagnosed, treated, and/or prevented with the

compositions of the invention include, but are not limited to, achondroplasia, atlanto-occipital fusion, arthrogryposis mulitplex congenita, autosomal recessive muscular dystrophy, Becker's muscular dystrophy, cerebral palsy, choanal atresia, cleft lip, cleft palate, clubfoot, congenital amputation, congenital dislocation of the hip, congenital torticollis, congenital scoliosis, dopa-repsonsive dystonia, Duchenne muscular dystrophy, early-onset generalized dystonia, femoral torsion, Gorlin syndrome, hypophosphatasia, Klippel-Feil syndrome, knee dislocation, myoclonic dystonia, myotonic dystrophy, nail-patella syndrome, osteogenesis imperfecta, paroxysmal dystonia, progeria, prune-belly syndrome, rapid-onset dystonia parkinsonism, scolosis, syndactyly, Treacher Collins' syndrome, velocardiofacial syndrome, and X-linked dystonia-parkinsonism.

[0638] Developmental or hereditary disorders or defects of the excretory system that may be diagnosed, treated, and/or prevented with the compositions of the invention include, but are not limited to, Alport's syndrome, Bartter's syndrome, bladder diverticula, bladder exstrophy, cystinuria, epispadias, Fanconi's syndrome, Hartnup disease, horseshoe kidney, hypospadias, kidney agenesis, kidney ectopia, kidney malrotation, Liddle's syndrome, medullary cystic disease, medullary sponge, multicystic kidney, kidney polycystic kidney disease, nail-patella syndrome, Potter's syndrome, urinary tract flow obstruction, vitamin D-resistant rickets, and Wilm's tumor.

[0639] Cardiovascular disorders or defects of developmental or hereditary origin that may be diagnosed, treated, and/or prevented with the compositions of the inventtion include, but are not limited to, aortic valve stenosis, atrial septal defects, artioventricular (A-V) canal defect, bicuspid aortic valve, coarctation or the aorta, dextrocardia, Ebstein's anomaly, Eisenmenger's complex, hypoplastic left heart syndrome, Marfan syndrome, patent ductus arteriosus, progeria, pulmonary atresia, pulmonary valve stenosis, subaortic stenosis, tetralogy of fallot, total anomalous pulmonary venous (P-V) connection, transposition of the great arteries, tricuspid atresia, truncus arteriosus, ventricular septal defects. Developmental or inherited disorders resulting in disorders involving the hematopoietic system that may be diagnosed, treated, and/or prevented with the compositions of the invention include, but not limited to, Bernard-Soulier syndrome, Chédiak-Higashi syndrome, hemophilia, Hermansky-Pudlak syndrome, sickle cell anemia, storage pool disease, thromboxane A2 dysfunction, thrombasthenia, and von Willebrand's disease.

[0640] The compositions of the invention may also be used to diagnose, treat, and/or prevent developmental and inherited disorders resulting in disorders or defects of the gastrointestinal system, including, but not limited to, anal atresia, biliary atresia, esophageal atresia, diaphragmatic hernia, Hirschsprung's disease, Meckel's diverticulum, oligohydramnios, omphalocele, polyhydramnios, porphyria, situs inversus viscera. Developmental or inherited disorders resulting in metabolic disorders that may be diagnosed, treated, and/or prevented with the compositions of the invention include, but are not limited to, alpha-1 antitrypsin deficiency, cystic fibrosis, hemochromatosis, lysosomal storage disease, phenylketonuria, Wilson's disease, and Zellweger syndrome.

[0641] Disorders of the reproductive system that are developmentally or hereditary related that may also be diagnosed, treated, and/or prevented with the compositions of the invention include, but are not limited to, androgen insensitivity syndrome, ambiguous genitalia, autosomal sex reversal, congenital adreneal hyperplasia, gonadoblastoma, ovarian germ cell cancer, pseudohermphroditism, true hermaphroditism, undescended testis, XX male syndrome, and XY female type gonadal dysgenesis. The compositions of the invention may also be used to diagnose, treat, and/or prevent developmental or inherited respiratory defects including, but not limited to, askin tumor, azygos lobe, congenital diaphragmatic hernia, congenital lobar emphysema, cystic adenomatoid malformation, lobar emphysema, hyaline membrane disease, and pectus excavatum.

[0642] Developmental or inherited disorders may also result from chromosomal or genetic aberration that may be diagnosed, treated, and/or prevented with the compositions of the invention including, but not limited to, 4p- syndrome, cri du chat syndrome, Digeorge syndrome, Down's syndrome, Edward's syndrome, fragile X syndrome, Klinefelter's syndrome, Patau's syndrome, Prader-Willi syndrome, progeria, Turner's syndrome, triple X syndrome, and XYY syndrome. Other developmental disorders that can be diagnosed, treated, and/or prevented with the compositions of the invention, include, but are not limited to, fetal alcohol syndrome, and can be caused by environmental factors surrounding the developing fetus.

[0643] The compositions of the invention may further be able to be used to diagnose, treat, and/or prevent errors in development or a genetic disposition that may result in hyperproliferative disorders or neoplasms, including, but not limited to, acute childhood lymphoblastic leukemia, askin tumor, Beckwith-Wiedemann syndrome,

childhood acute myeloid leukemia, childhood brain stem glioma, childhood cerebellar astrocytoma, childhood extracranial germ cell tumors childhood (primary), gonadoblastoma, hepatocellular cancer, childhood Hodgkin's disease, childhood Hodgkin's lymphoma, childhood hypothalamic and visual pathway glioma, childhood (primary) liver cancer, childhood lymphoblastic leukemia, childhood medulloblastoma, childhood non-Hodgkin's lymphoma, childhood pineal and supratentorial primitive neuroectodermal tumors, childhood primary liver cancer, childhood rhabdomyosarcoma, childhood soft tissue sarcoma, Gorlin syndrome, familial multiple endrocrine neoplasia type I, neuroblastoma, ovarian germ cell cancer, pheochromocytoma, retinoblastoma, and Wilm's tumor.

[0644] Polypeptides may be administered using any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, biolistic injectors, particle accelerators, gelfoam sponge depots, other commercially available depot materials, osmotic pumps, oral or suppositorial solid pharmaceutical formulations, decanting or topical applications during surgery, aerosol delivery. Such methods are known in the art. Polypeptides may be administered as part of a Therapeutic, described in more detail below. Methods of delivering polynucleotides are described in more detail herein.

Diseases at the Cellular Level

[0645] Diseases associated with increased cell survival or the inhibition of apoptosis that could be treated or detected by polynucleotides or polypeptides, as well as antagonists or agonists of the present invention, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer, prostate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) and viral infections (such as herpes viruses,

pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection. In preferred embodiments, polynucleotides, polypeptides, and/or antagonists of the invention are used to inhibit growth, progression, and/or metasis of cancers, in particular those listed above.

[0646] Additional diseases or conditions associated with increased cell survival that could be treated or detected by polynucleotides or polypeptides, or agonists or antagonists of the present invention include, but are not limited to, progression, and/or metastases of malignancies and related disorders such as leukemia (including acute leukemias (e.g., acute lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (e.g., chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (e.g., Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma, and retinoblastoma.

[0647] Diseases associated with increased apoptosis that could be treated or detected by polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, include AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Retinitis pigmentosa, Cerebellar degeneration and brain tumor or prior associated disease); autoimmune

disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) myelodysplastic syndromes (such as aplastic anemia), graft v. host disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestosis (bile duct injury) and liver cancer); toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

Wound Healing and Epithelial Cell Proliferation

[0648] In accordance with yet a further aspect of the present invention, there is provided a process for utilizing polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, for therapeutic purposes, for example, to stimulate epithelial cell proliferation and basal keratinocytes for the purpose of wound healing, and to stimulate hair follicle production and healing of dermal wounds. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may be clinically useful in stimulating wound healing including surgical wounds, excisional wounds, deep wounds involving damage of the dermis and epidermis, eye tissue wounds, dental tissue wounds, oral cavity wounds, diabetic ulcers, dermal ulcers, cubitus ulcers, arterial ulcers, venous stasis ulcers, burns resulting from heat exposure or chemicals, and other abnormal wound healing conditions such as uremia, malnutrition, vitamin deficiencies and complications associted with systemic treatment with steroids, radiation therapy and antineoplastic drugs and antimetabolites. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to promote dermal reestablishment subsequent to dermal loss

[0649] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to increase the adherence of skin grafts to a wound bed and to stimulate re-epithelialization from the wound bed. The following are types of grafts that polynucleotides or polypeptides, agonists or antagonists of the present invention, could be used to increase adherence to a wound bed: autografts, artificial skin, allografts, autodermic graft, autoepdermic grafts, avacular grafts, Blair-Brown grafts, bone graft, brephoplastic grafts, cutis graft, delayed graft, dermic graft, epidermic graft, fascia

graft, full thickness graft, heterologous graft, xenograft, homologous graft, hyperplastic graft, lamellar graft, mesh graft, mucosal graft, Ollier-Thiersch graft, omenpal graft, patch graft, pedicle graft, penetrating graft, split skin graft, thick split graft. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, can be used to promote skin strength and to improve the appearance of aged skin.

[0650] It is believed that polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, will also produce changes in hepatocyte proliferation, and epithelial cell proliferation in the lung, breast, pancreas, stomach, small intesting, and large intestine. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could promote proliferation of epithelial cells such as sebocytes, hair follicles, hepatocytes, type II pneumocytes, mucin-producing goblet cells, and other epithelial cells and their progenitors contained within the skin, lung, liver, and gastrointestinal tract. Polynucleotides or polypeptides, agonists or antagonists of the present invention, may promote proliferation of endothelial cells, keratinocytes, and basal keratinocytes.

[0651] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could also be used to reduce the side effects of gut toxicity that result from radiation, chemotherapy treatments or viral infections. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may have a cytoprotective effect on the small intestine mucosa. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may also stimulate healing of mucositis (mouth ulcers) that result from chemotherapy and viral infections.

[0652] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could further be used in full regeneration of skin in full and partial thickness skin defects, including burns, (i.e., repopulation of hair follicles, sweat glands, and sebaceous glands), treatment of other skin defects such as psoriasis. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat epidermolysis bullosa, a defect in adherence of the epidermis to the underlying dermis which results in frequent, open and painful blisters by accelerating reepithelialization of these lesions. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could also be used to treat gastric and doudenal ulcers and help heal by scar formation of the mucosal lining and regeneration of glandular

mucosa and duodenal mucosal lining more rapidly. Inflamamatory bowel diseases, such as Crohn's disease and ulcerative colitis, are diseases which result in destruction of the mucosal surface of the small or large intestine, respectively. Thus, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to promote the resurfacing of the mucosal surface to aid more rapid healing and to prevent progression of inflammatory bowel disease. Treatment with polynucleotides or polypeptides, agonists or antagonists of the present invention, is expected to have a significant effect on the production of mucus throughout the gastrointestinal tract and could be used to protect the intestinal mucosa from injurious substances that are ingested or following surgery. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat diseases associate with the under expression.

[0653] Moreover, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to prevent and heal damage to the lungs due to various pathological states. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, which could stimulate proliferation and differentiation and promote the repair of alveoli and brochiolar epithelium to prevent or treat acute or chronic lung damage. For example, emphysema, which results in the progressive loss of aveoli, and inhalation injuries, i.e., resulting from smoke inhalation and burns, that cause necrosis of the bronchiolar epithelium and alveoli could be effectively treated using polynucleotides or polypeptides, agonists or antagonists of the present invention. Also, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to stimulate the proliferation of and differentiation of type II pneumocytes, which may help treat or prevent disease such as hyaline membrane diseases, such as infant respiratory distress syndrome and bronchopulmonary displasia, in premature infants.

[0654] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could stimulate the proliferation and differentiation of hepatocytes and, thus, could be used to alleviate or treat liver diseases and pathologies such as fulminant liver failure caused by cirrhosis, liver damage caused by viral hepatitis and toxic substances (i.e., acetaminophen, carbon tetraholoride and other hepatotoxins known in the art).

[0655] In addition, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used treat or prevent the onset of diabetes mellitus. In patients with newly diagnosed Types I and II diabetes, where some islet cell function remains, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to maintain the islet function so as to alleviate, delay or prevent permanent manifestation of the disease. Also, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used as an auxiliary in islet cell transplantation to improve or promote islet cell function.

Infectious Disease

[0656] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention can be used to treat or detect infectious agents. For example, by increasing the immune response, particularly increasing the proliferation and differentiation of B and/or T cells, infectious diseases may be treated. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may also directly inhibit the infectious agent, without necessarily eliciting an immune response.

[0657] Viruses are one example of an infectious agent that can cause disease or symptoms that can be treated or detected by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention. Examples of viruses, include, but are not limited to Examples of viruses, include, but are not limited to the following DNA and RNA viruses and viral families: Arbovirus, Adenoviridae, Arenaviridae, Arterivirus, Birnaviridae, Bunyaviridae, Caliciviridae, Circoviridae, Coronaviridae, Dengue, EBV, HIV, Flaviviridae, Hepadnaviridae (Hepatitis), Herpesviridae (such as, Cytomegalovirus, Herpes Simplex, Herpes Zoster), Mononegavirus (e.g., Paramyxoviridae, Morbillivirus, Rhabdoviridae), Orthomyxoviridae (e.g., Influenza A, Influenza B, and parainfluenza), Papiloma virus, Papovaviridae, Parvoviridae, Picornaviridae, Poxviridae (such as Smallpox or Vaccinia), Reoviridae (e.g., Rotavirus), Retroviridae (HTLV-I, HTLV-II, Lentivirus), and Togaviridae (e.g., Rubivirus). Viruses falling within these families can cause a variety of diseases or symptoms, including, but not limited to: arthritis, bronchiollitis, respiratory syncytial virus, encephalitis, eye infections (e.g., conjunctivitis,

keratitis), chronic fatigue syndrome, hepatitis (A, B, C, E, Chronic Active, Delta), Japanese B encephalitis, Junin, Chikungunya, Rift Valley fever, yellow fever, meningitis, opportunistic infections (e.g., AIDS), pneumonia, Burkitt's Lymphoma, chickenpox, hemorrhagic fever, Measles, Mumps, Parainfluenza, Rabies, the common cold, Polio, leukemia, Rubella, sexually transmitted diseases, skin diseases (e.g., Kaposi's, warts), and viremia. polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used to treat or detect any of these symptoms or diseases. In specific embodiments, polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat: meningitis, Dengue, EBV, and/or hepatitis (e.g., hepatitis B). In an additional specific embodiment polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat patients nonresponsive to one or more other commercially available hepatitis vaccines. In a further specific embodiment polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat AIDS.

[0658] Similarly, bacterial or fungal agents that can cause disease or symptoms and that can be treated or detected by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention include, but are not limited to, the following Gram-Negative and Gram-positive bacteria, bacterial families, and fungi: Actinomyces (e.g., Norcardia), Acinetobacter, *Cryptococcus neoformans*, Aspergillus, Bacillaceae (e.g., *Bacillus anthrasis*), Bacteroides (e.g., *Bacteroides fragilis*), Blastomycosis, Bordetella, Borrelia (e.g., *Borrelia burgdorferi*), Brucella, Candidia, Campylobacter, Chlamydia, Clostridium (e.g., *Clostridium botulinum*, *Clostridium dificile*, *Clostridium perfringens*, *Clostridium tetani*), Coccidioides, Corynebacterium (e.g., *Corynebacterium diptheriae*), Cryptococcus, Dermatocycoses, *E. coli* (e.g., Enterotoxigenic *E. coli* and Enterohemorrhagic *E. coli*), Enterobacter (e.g. *Enterobacter aerogenes*), Enterobacteriaceae (Klebsiella, Salmonella (e.g., *Salmonella typhi*, *Salmonella enteritidis*, *Salmonella paratyphi*), Serratia, Yersinia, Shigella), Erysipelothrix, Haemophilus (e.g., *Haemophilus influenza* type B), Helicobacter, Legionella (e.g., *Legionella pneumophila*), Leptospira, Listeria (e.g., *Listeria monocytogenes*), Mycoplasma, Mycobacterium (e.g., *Mycobacterium leprae* and *Mycobacterium tuberculosis*), Vibrio (e.g.,*Vibrio cholerae*), Neisseriaceae (e.g., *Neisseria gonorrhea, Neisseria meningitidis*), Pasteurellacea, Proteus, Pseudomonas (e.g., *Psuedomonas aeruginosa*), Rickettsiaceae, Spirochetes (e.g., Treponema spp., Leptospira spp., Borrelia spp.) Shigella spp., Staphylococcus (e.g.,

Staphylococcus aureus), Meningiococcus, Pneumococcus and Streptococcus (e.g., *Streptococcus pneumoniae* and Groups A,B, and C Streptococci), and Ureaplasmas. These bacterial, parasitic, and fungal families can cause diseases or symptoms, including, but not limited to: antibiotic-resistant infections, bacteremia, endocarditis, septicemia, eye infections (conjunctivitis) tuberculosis, uveitis, gingivitis, bacterial diarrhea, opportunistic infections (e.g., AIDS related infections), paronychia, prosthesis-related infections, dental caries, Reiter's Disease, respiratory tract infections (e.g., Whooping Cough or Empyema), sepsis, Lyme Disease, Cat-Scratch Disease, dysentery, paratyphoid fever, food poisoning, Legionella disease, chronic and acute inflammation, erythema, yeast infections, typhoid, pneumonia, gonorrhea, meningitis (e.g., meningitis types A and B), chlamydia, syphilis, diphtheria, leprosy, burcellosis, peptic ulcers, anthrax, spontaneous abortion, birth defects, lung infections, ear infections, deafness, blindness, lethargy, malaise, vomiting, chronic diarrhea, Crohn's disease, colitis, vaginosis, sterility, pelvic inflammatory disease, candidiasis, paratuberculosis, tuberculosis, lupus, botulism, gangrene, tetanus, impetigo, Rheumatic Fever, Scarlet Fever, sexually transmitted diseases, skin diseases (e.g., cellulitis, dermatocycoses), toxemia, urinary tract infections, wound infections or noscomial infections. Polynucleotides or polypeptides, agonists or antagonists of the invention, can be used to treat or detect any of these symptoms or diseases. In specific embodiments, polynucleotides, polypeptides, agonists or antagonists of the invention are used to treat: tetanus, diptheria, botulism, and/or meningitis type B.

[0659] Moreover, parasitic agents causing disease or symptoms that can be treated or detected by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention include, but not limited to, the following families or class: Amebiasis, Babesiosis, Coccidiosis, Cryptosporidiosis, Dientamoebiasis, Dourine, Ectoparasitic, Giardiasis, Helminthiasis, Leishmaniasis, Theileriasis, Toxoplasmosis, Trypanosomiasis, and Trichomonas and Sporozoans (e.g., Plasmodium virax, Plasmodium falciparium, Plasmodium malariae and Plasmodium ovale). These parasites can cause a variety of diseases or symptoms, including, but not limited to: Scabies, Trombiculiasis, eye infections, intestinal disease (e.g., dysentery, giardiasis), liver disease, lung disease, opportunistic infections (e.g., AIDS related), malaria, pregnancy complications, and toxoplasmosis. polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used to treat or detect any of these symptoms or diseases.

[0660] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention of the present invention could either be by administering an effective amount of a polypeptide to the patient, or by removing cells from the patient, supplying the cells with a polynucleotide of the present invention, and returning the engineered cells to the patient (*ex vivo* therapy). Moreover, the polypeptide or polynucleotide of the present invention can be used as an antigen in a vaccine to raise an immune response against infectious disease.

Regeneration

[0661] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention can be used to differentiate, proliferate, and attract cells, leading to the regeneration of tissues. (See, Science 276:59-87 (1997).) The regeneration of tissues could be used to repair, replace, or protect tissue damaged by congenital defects, trauma (wounds, burns, incisions, or ulcers), age, disease (e.g. osteoporosis, osteocarthritis, periodontal disease, liver failure), surgery, including cosmetic plastic surgery, fibrosis, reperfusion injury, or systemic cytokine damage.

[0662] Tissues that could be regenerated using the present invention include organs (e.g., pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac), vasculature (including vascular and lymphatics), nervous, hematopoietic, and skeletal (bone, cartilage, tendon, and ligament) tissue. Preferably, regeneration occurs without or decreased scarring. Regeneration also may include angiogenesis.

[0663] Moreover, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may increase regeneration of tissues difficult to heal. For example, increased tendon/ligament regeneration would quicken recovery time after damage. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention could also be used prophylactically in an effort to avoid damage. Specific diseases that could be treated include of tendinitis, carpal tunnel syndrome, and other tendon or ligament defects. A further example of tissue regeneration of non-healing wounds includes pressure ulcers, ulcers associatedwith vascular insufficiency, surgical, and traumatic wounds.

[0664] Similarly, nerve and brain tissue could also be regenerated by using polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, to proliferate and differentiate nerve cells. Diseases that could be treated using this method include central and peripheral nervous system diseases, neuropathies, or mechanical and traumatic disorders (e.g., spinal cord disorders, head trauma, cerebrovascular disease, and stoke). Specifically, diseases associated with peripheral nerve injuries, peripheral neuropathy (e.g., resulting from chemotherapy or other medical therapies), localized neuropathies, and central nervous system diseases (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome), could all be treated using the polynucleotides or polypeptides, as well as agonists or antagonists of the present invention.

Chemotaxis

[0665] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may have chemotaxis activity. A chemotaxic molecule attracts or mobilizes cells (e.g., monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells) to a particular site in the body, such as inflammation, infection, or site of hyperproliferation. The mobilized cells can then fight off and/or heal the particular trauma or abnormality.

[0666] Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may increase chemotaxic activity of particular cells. These chemotactic molecules can then be used to treat inflammation, infection, hyperproliferative disorders, or any immune system disorder by increasing the number of cells targeted to a particular location in the body. For example, chemotaxic molecules can be used to treat wounds and other trauma to tissues by attracting immune cells to the injured location. Chemotactic molecules of the present invention can also attract fibroblasts, which can be used to treat wounds.

[0667] It is also contemplated that polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may inhibit chemotactic activity. These molecules could also be used to treat disorders. Thus, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention could be used as an inhibitor of chemotaxis.

Binding Activity

[0668] A polypeptide of the present invention may be used to screen for molecules that bind to the polypeptide or for molecules to which the polypeptide binds. The binding of the polypeptide and the molecule may activate (agonist), increase, inhibit (antagonist), or decrease activity of the polypeptide or the molecule bound. Examples of such molecules include antibodies, oligonucleotides, proteins (e.g., receptors),or small molecules.

[0669] Preferably, the molecule is closely related to the natural ligand of the polypeptide, e.g., a fragment of the ligand, or a natural substrate, a ligand, a structural or functional mimetic. (See, Coligan et al., Current Protocols in Immunology 1(2):Chapter 5 (1991).) Similarly, the molecule can be closely related to the natural receptor to which the polypeptide binds, or at least, a fragment of the receptor capable of being bound by the polypeptide (e.g., active site). In either case, the molecule can be rationally designed using known techniques.

[0670] Preferably, the screening for these molecules involves producing appropriate cells which express the polypeptide. Preferred cells include cells from mammals, yeast, Drosophila, or *E. coli*. Cells expressing the polypeptide (or cell membrane containing the expressed polypeptide) are then preferably contacted with a test compound potentially containing the molecule to observe binding, stimulation, or inhibition of activity of either the polypeptide or the molecule.

[0671] The assay may simply test binding of a candidate compound to the polypeptide, wherein binding is detected by a label, or in an assay involving competition with a labeled competitor. Further, the assay may test whether the candidate compound results in a signal generated by binding to the polypeptide.

[0672] Alternatively, the assay can be carried out using cell-free preparations, polypeptide/molecule affixed to a solid support, chemical libraries, or natural product mixtures. The assay may also simply comprise the steps of mixing a candidate compound with a solution containing a polypeptide, measuring polypeptide/molecule activity or binding, and comparing the polypeptide/molecule activity or binding to a standard.

[0673] Preferably, an ELISA assay can measure polypeptide level or activity in a sample (e.g., biological sample) using a monoclonal or polyclonal antibody. The antibody

can measure polypeptide level or activity by either binding, directly or indirectly, to the polypeptide or by competing with the polypeptide for a substrate.

[0674] Additionally, the receptor to which the polypeptide of the present invention binds can be identified by numerous methods known to those of skill in the art, for example, ligand panning and FACS sorting (Coligan, et al., Current Protocols in Immun., 1(2), Chapter 5, (1991)). For example, expression cloning is employed wherein polyadenylated RNA is prepared from a cell responsive to the polypeptides, for example, NIH3T3 cells which are known to contain multiple receptors for the FGF family proteins, and SC-3 cells, and a cDNA library created from this RNA is divided into pools and used to transfect COS cells or other cells that are not responsive to the polypeptides. Transfected cells which are grown on glass slides are exposed to the polypeptide of the present invention, after they have been labelled. The polypeptides can be labeled by a variety of means including iodination or inclusion of a recognition site for a site-specific protein kinase.

[0675] Following fixation and incubation, the slides are subjected to auto-radiographic analysis. Positive pools are identified and sub-pools are prepared and re-transfected using an iterative sub-pooling and re-screening process, eventually yielding a single clones that encodes the putative receptor.

[0676] As an alternative approach for receptor identification, the labeled polypeptides can be photoaffinity linked with cell membrane or extract preparations that express the receptor molecule. Cross-linked material is resolved by PAGE analysis and exposed to X-ray film. The labeled complex containing the receptors of the polypeptides can be excised, resolved into peptide fragments, and subjected to protein microsequencing. The amino acid sequence obtained from microsequencing would be used to design a set of degenerate oligonucleotide probes to screen a cDNA library to identify the genes encoding the putative receptors.

[0677] Moreover, the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling") may be employed to modulate the activities of the polypeptide of the present invention thereby effectively generating agonists and antagonists of the polypeptide of the present invention. *See generally*, U.S. Patent Nos. 5,605,793, 5,811,238, 5,830,721, 5,834,252, and 5,837,458, and Patten, P. A., *et al., Curr. Opinion Biotechnol.* 8:724-33 (1997);

Harayama, S. *Trends Biotechnol.* 16(2):76-82 (1998); Hansson, L. O., *et al., J. Mol. Biol.* 287:265-76 (1999); and Lorenzo, M. M. and Blasco, R. *Biotechniques* 24(2):308-13 (1998) (each of these patents and publications are hereby incorporated by reference). In one embodiment, alteration of polynucleotides and corresponding polypeptides may be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments into a desired molecule by homologous, or site-specific, recombination. In another embodiment, polynucleotides and corresponding polypeptides may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of the polypeptide of the present invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules. In preferred embodiments, the heterologous molecules are family members. In further preferred embodiments, the heterologous molecule is a growth factor such as, for example, platelet-derived growth factor (PDGF), insulin-like growth factor (IGF-I), transforming growth factor (TGF)-alpha, epidermal growth factor (EGF), fibroblast growth factor (FGF), TGF-beta, bone morphogenetic protein (BMP)-2, BMP-4, BMP-5, BMP-6, BMP-7, activins A and B, decapentaplegic(dpp), 60A, OP-2, dorsalin, growth differentiation factors (GDFs), nodal, MIS, inhibin-alpha, TGF-beta1, TGF-beta2, TGF-beta3, TGF-beta5, and glial-derived neurotrophic factor (GDNF).

[0678] Other preferred fragments are biologically active fragments of the polypeptide of the present invention. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

[0679] Additionally, this invention provides a method of screening compounds to identify those which modulate the action of the polypeptide of the present invention. An example of such an assay comprises combining a mammalian fibroblast cell, a the polypeptide of the present invention, the compound to be screened and ^{3}[H] thymidine under cell culture conditions where the fibroblast cell would normally proliferate. A control assay may be performed in the absence of the compound to be screened and compared to the amount of fibroblast proliferation in the presence of the compound to

determine if the compound stimulates proliferation by determining the uptake of ^{3}[H] thymidine in each case. The amount of fibroblast cell proliferation is measured by liquid scintillation chromatography which measures the incorporation of ^{3}[H] thymidine. Both agonist and antagonist compounds may be identified by this procedure.

[0680] In another method, a mammalian cell or membrane preparation expressing a receptor for a polypeptide of the present invention is incubated with a labeled polypeptide of the present invention in the presence of the compound. The ability of the compound to enhance or block this interaction could then be measured. Alternatively, the response of a known second messenger system following interaction of a compound to be screened and the receptor is measured and the ability of the compound to bind to the receptor and elicit a second messenger response is measured to determine if the compound is a potential agonist or antagonist. Such second messenger systems include but are not limited to, cAMP guanylate cyclase, ion channels or phosphoinositide hydrolysis.

[0681] All of these above assays can be used as diagnostic or prognostic markers. The molecules discovered using these assays can be used to treat disease or to bring about a particular result in a patient (e.g., blood vessel growth) by activating or inhibiting the polypeptide/molecule. Moreover, the assays can discover agents which may inhibit or enhance the production of the polypeptides of the invention from suitably manipulated cells or tissues.

[0682] Therefore, the invention includes a method of identifying compounds which bind to a polypeptide of the invention comprising the steps of: (a) incubating a candidate binding compound with a polypeptide of the present invention; and (b) determining if binding has occurred. Moreover, the invention includes a method of identifying agonists/antagonists comprising the steps of: (a) incubating a candidate compound with a polypeptide of the present invention, (b) assaying a biological activity, and (b) determining if a biological activity of the polypeptide has been altered.

Targeted Delivery

[0683] In another embodiment, the invention provides a method of delivering compositions to targeted cells expressing a receptor for a polypeptide of the invention, or cells expressing a cell bound form of a polypeptide of the invention.

[0684] As discussed herein, polypeptides or antibodies of the invention may be associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs via hydrophobic, hydrophilic, ionic and/or covalent interactions. In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells by administering polypeptides of the invention (including antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

[0685] In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention (e.g., polypeptides of the invention or antibodies of the invention) in association with toxins or cytotoxic prodrugs.

[0686] By "toxin" is meant compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNAse, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. By "cytotoxic prodrug" is meant a non-toxic compound that is converted by an enzyme, normally present in the cell, into a cytotoxic compound. Cytotoxic prodrugs that may be used according to the methods of the invention include, but are not limited to, glutamyl derivatives of benzoic acid mustard alkylating agent, phosphate derivatives of etoposide or mitomycin C, cytosine arabinoside, daunorubisin, and phenoxyacetamide derivatives of doxorubicin.

Drug Screening

[0687] Further contemplated is the use of the polypeptides of the present invention, or the polynucleotides encoding these polypeptides, to screen for molecules which modify the activities of the polypeptides of the present invention. Such a method would include contacting the polypeptide of the present invention with a selected compound(s) suspected of having antagonist or agonist activity, and assaying the activity of these polypeptides following binding.

[0688] This invention is particularly useful for screening therapeutic compounds by using the polypeptides of the present invention, or binding fragments thereof, in any of a variety of drug screening techniques. The polypeptide or fragment employed in such a test may be affixed to a solid support, expressed on a cell surface, free in solution, or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the polypeptide or fragment. Drugs are screened against such transformed cells in competitive binding assays. One may measure, for example, the formulation of complexes between the agent being tested and a polypeptide of the present invention.

[0689] Thus, the present invention provides methods of screening for drugs or any other agents which affect activities mediated by the polypeptides of the present invention. These methods comprise contacting such an agent with a polypeptide of the present invention or a fragment thereof and assaying for the presence of a complex between the agent and the polypeptide or a fragment thereof, by methods well known in the art. In such a competitive binding assay, the agents to screen are typically labeled. Following incubation, free agent is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of a particular agent to bind to the polypeptides of the present invention.

[0690] Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to the polypeptides of the present invention, and is described in great detail in European Patent Application 84/03564, published on September 13, 1984, which is incorporated herein by reference herein. Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. The peptide test compounds

are reacted with polypeptides of the present invention and washed. Bound polypeptides are then detected by methods well known in the art. Purified polypeptides are coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies may be used to capture the peptide and immobilize it on the solid support.

[0691] This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding polypeptides of the present invention specifically compete with a test compound for binding to the polypeptides or fragments thereof. In this manner, the antibodies are used to detect the presence of any peptide which shares one or more antigenic epitopes with a polypeptide of the invention.

<u>Antisense And Ribozyme (Antagonists)</u>

[0692] In specific embodiments, antagonists according to the present invention are nucleic acids corresponding to the sequences contained in SEQ ID NO:X, or the complementary strand thereof, and/or to nucleotide sequences contained in the cDNA contained in the related cDNA clone identified in Table 1. In one embodiment, antisense sequence is generated internally, by the organism, in another embodiment, the antisense sequence is separately administered (see, for example, O'Connor, J., Neurochem. 56:560 (1991). Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Antisense technology can be used to control gene expression through antisense DNA or RNA, or through triple-helix formation. Antisense techniques are discussed for example, in Okano, J., Neurochem. 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance, Lee et al., Nucleic Acids Research 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1300 (1991). The methods are based on binding of a polynucleotide to a complementary DNA or RNA.

[0693] For example, the use of c-myc and c-myb antisense RNA constructs to inhibit the growth of the non-lymphocytic leukemia cell line HL-60 and other cell lines was previously described. (Wickstrom et al. (1988); Anfossi et al. (1989)). These experiments were performed in vitro by incubating cells with the oligoribonucleotide. A similar procedure for in vivo use is described in WO 91/15580. Briefly, a pair of

oligonucleotides for a given antisense RNA is produced as follows: A sequence complimentary to the first 15 bases of the open reading frame is flanked by an EcoR1 site on the 5 end and a HindIII site on the 3 end. Next, the pair of oligonucleotides is heated at 90°C for one minute and then annealed in 2X ligation buffer (20mM TRIS HCl pH 7.5, 10mM MgCl2, 10MM dithiothreitol (DTT) and 0.2 mM ATP) and then ligated to the EcoR1/Hind III site of the retroviral vector PMV7 (WO 91/15580).

[0694] For example, the 5' coding portion of a polynucleotide that encodes the polypeptide of the present invention may be used to design an antisense RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription thereby preventing transcription and the production of the receptor. The antisense RNA oligonucleotide hybridizes to the mRNA in vivo and blocks translation of the mRNA molecule into receptor polypeptide.

[0695] In one embodiment, the antisense nucleic acid of the invention is produced intracellularly by transcription from an exogenous sequence. For example, a vector or a portion thereof, is transcribed, producing an antisense nucleic acid (RNA) of the invention. Such a vector would contain a sequence encoding the antisense nucleic acid. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral, or others known in the art, used for replication and expression in vertebrate cells. Expression of the sequence encoding the polypeptide of the present invnetion or fragments thereof, can be by any promoter known in the art to act in vertebrate, preferably human cells. Such promoters can be inducible or constitutive. Such promoters include, but are not limited to, the SV40 early promoter region (Bernoist and Chambon, Nature 29:304-310 (1981), the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto et al., Cell 22:787-797 (1980), the herpes thymidine promoter (Wagner et al., Proc. Natl. Acad. Sci. U.S.A. 78:1441-1445 (1981), the regulatory sequences of the metallothionein gene (Brinster, et al., Nature 296:39-42 (1982)), etc.

[0696] The antisense nucleic acids of the invention comprise a sequence complementary to at least a portion of an RNA transcript of a gene of the present invention. However, absolute complementarity, although preferred, is not required. A

sequence "complementary to at least a portion of an RNA," referred to herein, means a sequence having sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double stranded antisense nucleic acids, a single strand of the duplex DNA may thus be tested, or triplex formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid. Generally, the larger the hybridizing nucleic acid, the more base mismatches with a RNA it may contain and still form a stable duplex (or triplex as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures to determine the melting point of the hybridized complex.

[0697] Oligonucleotides that are complementary to the 5' end of the message, e.g., the 5' untranslated sequence up to and including the AUG initiation codon, should work most efficiently at inhibiting translation. However, sequences complementary to the 3' untranslated sequences of mRNAs have been shown to be effective at inhibiting translation of mRNAs as well. See generally, Wagner, R., 1994, Nature 372:333-335. Thus, oligonucleotides complementary to either the 5'- or 3'- non- translated, non-coding regions of polynucleotide sequences described herein could be used in an antisense approach to inhibit translation of endogenous mRNA. Oligonucleotides complementary to the 5' untranslated region of the mRNA should include the complement of the AUG start codon. Antisense oligonucleotides complementary to mRNA coding regions are less efficient inhibitors of translation but could be used in accordance with the invention. Whether designed to hybridize to the 5'-, 3'- or coding region of mRNA of the present invention, antisense nucleic acids should be at least six nucleotides in length, and are preferably oligonucleotides ranging from 6 to about 50 nucleotides in length. In specific aspects the oligonucleotide is at least 10 nucleotides, at least 17 nucleotides, at least 25 nucleotides or at least 50 nucleotides.

[0698] The polynucleotides of the invention can be DNA or RNA or chimeric mixtures or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or phosphate backbone, for example, to improve stability of the molecule, hybridization, etc. The oligonucleotide may include other appended groups such as peptides (e.g., for targeting host cell receptors in vivo), or agents facilitating transport across the cell membrane (see, e.g., Letsinger et al., 1989, Proc. Natl. Acad. Sci. U.S.A. 86:6553-6556; Lemaitre et al.,

1987, Proc. Natl. Acad. Sci. 84:648-652; PCT Publication No. WO88/09810, published December 15, 1988) or the blood-brain barrier (see, e.g., PCT Publication No. WO89/10134, published April 25, 1988), hybridization-triggered cleavage agents. (See, e.g., Krol et al., 1988, BioTechniques 6:958-976) or intercalating agents. (See, e.g., Zon, 1988, Pharm. Res. 5:539-549). To this end, the oligonucleotide may be conjugated to another molecule, e.g., a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

[0699] The antisense oligonucleotide may comprise at least one modified base moiety which is selected from the group including, but not limited to, 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xantine, 4-acetylcytosine, 5-(carboxyhydroxylmethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.

[0700] The antisense oligonucleotide may also comprise at least one modified sugar moiety selected from the group including, but not limited to, arabinose, 2-fluoroarabinose, xylulose, and hexose.

[0701] In yet another embodiment, the antisense oligonucleotide comprises at least one modified phosphate backbone selected from the group including, but not limited to, a phosphorothioate, a phosphorodithioate, a phosphoramidothioate, a phosphoramidate, a phosphordiamidate, a methylphosphonate, an alkyl phosphotriester, and a formacetal or analog thereof.

[0702] In yet another embodiment, the antisense oligonucleotide is an a-anomeric oligonucleotide. An a-anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual b-units, the strands run parallel to each other (Gautier et al., 1987, Nucl. Acids Res. 15:6625-6641). The oligonucleotide

is a 2'-0-methylribonucleotide (Inoue et al., 1987, Nucl. Acids Res. 15:6131-6148), or a chimeric RNA-DNA analogue (Inoue et al., 1987, FEBS Lett. 215:327-330).

[0703] Polynucleotides of the invention may be synthesized by standard methods known in the art, e.g. by use of an automated DNA synthesizer (such as are commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligonucleotides may be synthesized by the method of Stein et al. (1988, Nucl. Acids Res. 16:3209), methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports (Sarin et al., 1988, Proc. Natl. Acad. Sci. U.S.A. 85:7448-7451), etc.

[0704] While antisense nucleotides complementary to the coding region sequence could be used, those complementary to the transcribed untranslated region are most preferred.

[0705] Potential antagonists according to the invention also include catalytic RNA, or a ribozyme (See, e.g., PCT International Publication WO 90/11364, published October 4, 1990; Sarver et al, Science 247:1222-1225 (1990). While ribozymes that cleave mRNA at site specific recognition sequences can be used to destroy mRNAs, the use of hammerhead ribozymes is preferred. Hammerhead ribozymes cleave mRNAs at locations dictated by flanking regions that form complementary base pairs with the target mRNA. The sole requirement is that the target mRNA have the following sequence of two bases: 5'-UG-3'. The construction and production of hammerhead ribozymes is well known in the art and is described more fully in Haseloff and Gerlach, Nature 334:585-591 (1988). There are numerous potential hammerhead ribozyme cleavage sites within the nucleotide sequence of SEQ ID NO:X. Preferably, the ribozyme is engineered so that the cleavage recognition site is located near the 5' end of the mRNA; i.e., to increase efficiency and minimize the intracellular accumulation of non-functional mRNA transcripts.

[0706] As in the antisense approach, the ribozymes of the invention can be composed of modified oligonucleotides (e.g. for improved stability, targeting, etc.) and should be delivered to cells which express in vivo. DNA constructs encoding the ribozyme may be introduced into the cell in the same manner as described above for the introduction of antisense encoding DNA. A preferred method of delivery involves using a DNA construct "encoding" the ribozyme under the control of a strong constitutive promoter, such as, for example, pol III or pol II promoter, so that transfected cells will

produce sufficient quantities of the ribozyme to destroy endogenous messages and inhibit translation. Since ribozymes unlike antisense molecules, are catalytic, a lower intracellular concentration is required for efficiency.

[0707] Antagonist/agonist compounds may be employed to inhibit the cell growth and proliferation effects of the polypeptides of the present invention on neoplastic cells and tissues, i.e. stimulation of angiogenesis of tumors, and, therefore, retard or prevent abnormal cellular growth and proliferation, for example, in tumor formation or growth.

[0708] The antagonist/agonist may also be employed to prevent hyper-vascular diseases, and prevent the proliferation of epithelial lens cells after extracapsular cataract surgery. Prevention of the mitogenic activity of the polypeptides of the present invention may also be desirous in cases such as restenosis after balloon angioplasty.

[0709] The antagonist/agonist may also be employed to prevent the growth of scar tissue during wound healing.

[0710] The antagonist/agonist may also be employed to treat the diseases described herein.

[0711] Thus, the invention provides a method of treating disorders or diseases, including but not limited to the disorders or diseases listed throughout this application, associated with overexpression of a polynucleotide of the present invention by administering to a patient (a) an antisense molecule directed to the polynucleotide of the present invention, and/or (b) a ribozyme directed to the polynucleotide of the present invention.

Binding Peptides and Other Molecules

[0712] The invention also encompasses screening methods for identifying polypeptides and nonpolypeptides that bind prostate cancer antigen polypeptides, and the prostate cancer antigen binding molecules identified thereby. These binding molecules are useful, for example, as agonists and antagonists of the prostate cancer antigen polypeptides. Such agonists and antagonists can be used, in accordance with the invention, in the therapeutic embodiments described in detail, below.

[0713] This method comprises the steps of:

contacting prostate cancer antigen polypeptides or prostate cancer antigen-like polypeptides with a plurality of molecules; and

identifying a molecule that binds the prostate cancer antigen polypeptides or prostate cancer antigen-like polypeptides.

[0714] The step of contacting the prostate cancer antigen polypeptides or prostate cancer antigen-like polypeptides with the plurality of molecules may be effected in a number of ways. For example, one may contemplate immobilizing the prostate cancer antigen polypeptides or prostate cancer antigen-like polypeptides on a solid support and bringing a solution of the plurality of molecules in contact with the immobilized prostate cancer antigen polypeptides or prostate cancer antigen-like polypeptides. Such a procedure would be akin to an affinity chromatographic process, with the affinity matrix being comprised of the immobilized prostate cancer antigen polypeptides or prostate cancer antigen-like polypeptides. The molecules having a selective affinity for the prostate cancer antigen polypeptides or prostate cancer antigen-like polypeptides can then be purified by affinity selection. The nature of the solid support, process for attachment of the prostate cancer antigen polypeptides or prostate cancer antigen-like polypeptides to the solid support, solvent, and conditions of the affinity isolation or selection are largely conventional and well known to those of ordinary skill in the art.

[0715] Alternatively, one may also separate a plurality of polypeptides into substantially separate fractions comprising a subset of or individual polypeptides. For instance, one can separate the plurality of polypeptides by gel electrophoresis, column chromatography, or like method known to those of ordinary skill for the separation of polypeptides. The individual polypeptides can also be produced by a transformed host cell in such a way as to be expressed on or about its outer surface (e.g., a recombinant phage). Individual isolates can then be "probed" by the prostate cancer antigen polypeptides or prostate cancer antigen-like polypeptides, optionally in the presence of an inducer should one be required for expression, to determine if any selective affinity interaction takes place between the prostate cancer antigen polypeptides or prostate cancer antigen-like polypeptides and the individual clone. Prior to contacting the prostate cancer antigen polypeptides or prostate cancer antigen-like polypeptides with each fraction comprising individual polypeptides, the polypeptides could first be transferred to a solid support for additional convenience. Such a solid support may simply be a piece of filter membrane, such as one made of nitrocellulose or nylon. In this manner, positive clones could be identified from a collection of transformed host cells of an expression library, which

harbor a DNA construct encoding a polypeptide having a selective affinity for prostate cancer antigen polypeptides or prostate cancer antigen-like polypeptides. Furthermore, the amino acid sequence of the polypeptide having a selective affinity for the prostate cancer antigen polypeptides or prostate cancer antigen-like polypeptides can be determined directly by conventional means or the coding sequence of the DNA encoding the polypeptide can frequently be determined more conveniently. The primary sequence can then be deduced from the corresponding DNA sequence. If the amino acid sequence is to be determined from the polypeptide itself, one may use microsequencing techniques. The sequencing technique may include mass spectroscopy.

[0716] In certain situations, it may be desirable to wash away any unbound prostate cancer antigen polypeptides or prostate cancer antigen-like polypeptides, or alternatively, unbound polypeptides, from a mixture of the prostate cancer antigen polypeptides or prostate cancer antigen-like polypeptides and the plurality of polypeptides prior to attempting to determine or to detect the presence of a selective affinity interaction. Such a wash step may be particularly desirable when the prostate cancer antigen polypeptides or prostate cancer antigen-like polypeptides or the plurality of polypeptides is bound to a solid support.

[0717] The plurality of molecules provided according to this method may be provided by way of diversity libraries, such as random or combinatorial peptide or nonpeptide libraries which can be screened for molecules that specifically bind prostate cancer antigen polypeptides. Many libraries are known in the art that can be used, e.g., chemically synthesized libraries, recombinant (e.g., phage display libraries), and *in vitro* translation-based libraries. Examples of chemically synthesized libraries are described in Fodor et al., 1991, Science 251:767-773; Houghten et al., 1991, Nature 354:84-86; Lam et al., 1991, Nature 354:82-84; Medynski, 1994, Bio/Technology 12:709-710;Gallop et al., 1994, J. Medicinal Chemistry 37(9):1233-1251; Ohlmeyer et al., 1993, Proc. Natl. Acad. Sci. USA 90:10922-10926; Erb et al., 1994, Proc. Natl. Acad. Sci. USA 91:11422-11426; Houghten et al., 1992, Biotechniques 13:412; Jayawickreme et al., 1994, Proc. Natl. Acad. Sci. USA 91:1614-1618; Salmon et al., 1993, Proc. Natl. Acad. Sci. USA 90:11708-11712; PCT Publication No. WO 93/20242; and Brenner and Lerner, 1992, Proc. Natl. Acad. Sci. USA 89:5381-5383.

[0718] Examples of phage display libraries are described in Scott and Smith, 1990,

Science 249:386-390; Devlin et al., 1990, Science, 249:404-406; Christian, R. B., et al., 1992, J. Mol. Biol. 227:711-718); Lenstra, 1992, J. Immunol. Meth. 152:149-157; Kay et al., 1993, Gene 128:59-65; and PCT Publication No. WO 94/18318 dated Aug. 18, 1994.

[0719] *In vitro* translation-based libraries include but are not limited to those described in PCT Publication No. WO 91/05058 dated Apr. 18, 1991; and Mattheakis et al., 1994, Proc. Natl. Acad. Sci. USA 91:9022-9026.

[0720] By way of examples of nonpeptide libraries, a benzodiazepine library (see e.g., Bunin et al., 1994, Proc. Natl. Acad. Sci. USA 91:4708-4712) can be adapted for use. Peptoid libraries (Simon et al., 1992, Proc. Natl. Acad. Sci. USA 89:9367-9371) can also be used. Another example of a library that can be used, in which the amide functionalities in peptides have been permethylated to generate a chemically transformed combinatorial library, is described by Ostresh et al. (1994, Proc. Natl. Acad. Sci. USA 91:11138-11142).

[0721] The variety of non-peptide libraries that are useful in the present invention is great. For example, Ecker and Crooke, 1995, Bio/Technology 13:351-360 list benzodiazepines, hydantoins, piperazinediones, biphenyls, sugar analogs, beta-mercaptoketones, arylacetic acids, acylpiperidines, benzopyrans, cubanes, xanthines, aminimides, and oxazolones as among the chemical species that form the basis of various libraries.

[0722] Non-peptide libraries can be classified broadly into two types: decorated monomers and oligomers. Decorated monomer libraries employ a relatively simple scaffold structure upon which a variety functional groups is added. Often the scaffold will be a molecule with a known useful pharmacological activity. For example, the scaffold might be the benzodiazepine structure.

[0723] Non-peptide oligomer libraries utilize a large number of monomers that are assembled together in ways that create new shapes that depend on the order of the monomers. Among the monomer units that have been used are carbamates, pyrrolinones, and morpholinos. Peptoids, peptide-like oligomers in which the side chain is attached to the alpha amino group rather than the alpha carbon, form the basis of another version of non-peptide oligomer libraries. The first non-peptide oligomer libraries utilized a single type of monomer and thus contained a repeating backbone. Recent libraries have utilized more than one monomer, giving the libraries added flexibility.

[0724] Screening the libraries can be accomplished by any of a variety of

commonly known methods. See, e.g., the following references, which disclose screening of peptide libraries: Parmley and Smith, 1989, Adv. Exp. Med. Biol. 251:215-218; Scott and Smith, 1990, Science 249:386-390; Fowlkes et al., 1992; BioTechniques 13:422-427; Oldenburg et al., 1992, Proc. Natl. Acad. Sci. USA 89:5393-5397; Yu et al., 1994, Cell 76:933-945; Staudt et al., 1988, Science 241:577-580; Bock et al., 1992, Nature 355:564-566; Tuerk et al., 1992, Proc. Natl. Acad. Sci. USA 89:6988-6992; Ellington et al., 1992, Nature 355:850-852; U.S. Pat. No. 5,096,815, U.S. Pat. No. 5,223,409, and U.S. Pat. No. 5,198,346, all to Ladner et al.; Rebar and Pabo, 1993, Science 263:671-673; and CT Publication No. WO 94/18318.

[0725] In a specific embodiment, screening to identify a molecule that binds prostate cancer antigen polypeptides can be carried out by contacting the library members with a prostate cancer antigen polypeptides or prostate cancer antigen-like polypeptides immobilized on a solid phase and harvesting those library members that bind to the prostate cancer antigen polypeptides or prostate cancer antigen-like polypeptides. Examples of such screening methods, termed "panning" techniques are described by way of example in Parmley and Smith, 1988, Gene 73:305-318; Fowlkes et al., 1992, BioTechniques 13:422-427; International Publication No. WO 94/18318; and in references cited herein.

[0726] In another embodiment, the two-hybrid system for selecting interacting proteins in yeast (Fields and Song, 1989, Nature 340:245-246; Chien et al., 1991, Proc. Natl. Acad. Sci. USA 88:9578-9582) can be used to identify molecules that specifically bind to prostate cancer antigen polypeptides or prostate cancer antigen-like polypeptides.

[0727] Where the prostate cancer antigen binding molecule is a polypeptide, the polypeptide can be conveniently selected from any peptide library, including random peptide libraries, combinatorial peptide libraries, or biased peptide libraries. The term "biased" is used herein to mean that the method of generating the library is manipulated so as to restrict one or more parameters that govern the diversity of the resulting collection of molecules, in this case peptides.

[0728] Thus, a truly random peptide library would generate a collection of peptides in which the probability of finding a particular amino acid at a given position of the peptide is the same for all 20 amino acids. A bias can be introduced into the library, however, by specifying, for example, that a lysine occurs every fifth amino acid or that

positions 4, 8, and 9 of a decapeptide library be fixed to include only arginine. Clearly, many types of biases can be contemplated, and the present invention is not restricted to any particular bias. Furthermore, the present invention contemplates specific types of peptide libraries, such as phage displayed peptide libraries and those that utilize a DNA construct comprising a lambda phage vector with a DNA insert.

[0729] As mentioned above, in the case of a prostate cancer antigen binding molecule that is a polypeptide, the polypeptide may have about 6 to less than about 60 amino acid residues, preferably about 6 to about 10 amino acid residues, and most preferably, about 6 to about 22 amino acids. In another embodiment, a prostate cancer antigen binding polypeptide has in the range of 15-100 amino acids, or 20-50 amino acids.

[0730] The selected prostate cancer antigen binding polypeptide can be obtained by chemical synthesis or recombinant expression.

Other Activities

[0731] A polypeptide, polynucleotide, agonist, or antagonist of the present invention, as a result of the ability to stimulate vascular endothelial cell growth, may be employed in treatment for stimulating re-vascularization of ischemic tissues due to various disease conditions such as thrombosis, arteriosclerosis, and other cardiovascular conditions. The polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed to stimulate angiogenesis and limb regeneration, as discussed above.

[0732] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed for treating wounds due to injuries, burns, post-operative tissue repair, and ulcers since they are mitogenic to various cells of different origins, such as fibroblast cells and skeletal muscle cells, and therefore, facilitate the repair or replacement of damaged or diseased tissue.

[0733] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed stimulate neuronal growth and to treat and prevent neuronal damage which occurs in certain neuronal disorders or neuro-degenerative conditions such as Alzheimer's disease, Parkinson's disease, and AIDS-related complex. A polypeptide, polynucleotide, agonist, or antagonist of the present invention may have the

ability to stimulate chondrocyte growth, therefore, they may be employed to enhance bone and periodontal regeneration and aid in tissue transplants or bone grafts.

[0734] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may be also be employed to prevent skin aging due to sunburn by stimulating keratinocyte growth.

[0735] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed for preventing hair loss, since FGF family members activate hair-forming cells and promotes melanocyte growth. Along the same lines, a polypeptide, polynucleotide, agonist, or antagonist of the present invention may be employed to stimulate growth and differentiation of hematopoietic cells and bone marrow cells when used in combination with other cytokines.

[0736] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed to maintain organs before transplantation or for supporting cell culture of primary tissues. A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed for inducing tissue of mesodermal origin to differentiate in early embryos.

[0737] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also increase or decrease the differentiation or proliferation of embryonic stem cells, besides, as discussed above, hematopoietic lineage.

[0738] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be used to modulate mammalian characteristics, such as body height, weight, hair color, eye color, skin, percentage of adipose tissue, pigmentation, size, and shape (e.g., cosmetic surgery). Similarly, a polypeptide, polynucleotide, agonist, or antagonist of the present invention may be used to modulate mammalian metabolism affecting catabolism, anabolism, processing, utilization, and storage of energy.

[0739] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may be used to change a mammal's mental state or physical state by influencing biorhythms, caricadic rhythms, depression (including depressive disorders), tendency for violence, tolerance for pain, reproductive capabilities (preferably by Activin or Inhibin-like activity), hormonal or endocrine levels, appetite, libido, memory, stress, or other cognitive qualities.

[0740] A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be used as a food additive or preservative, such as to increase or decrease storage capabilities, fat content, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional components.

[0741] The above-recited applications have uses in a wide variety of hosts. Such hosts include, but are not limited to, human, murine, rabbit, goat, guinea pig, camel, horse, mouse, rat, hamster, pig, micro-pig, chicken, goat, cow, sheep, dog, cat, non-human primate, and human. In specific embodiments, the host is a mouse, rabbit, goat, guinea pig, chicken, rat, hamster, pig, sheep, dog or cat. In preferred embodiments, the host is a mammal. In most preferred embodiments, the host is a human.

Other Preferred Embodiments

[0742] Other preferred embodiments of the claimed invention include an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 50 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, and/or the cDNA in the related cDNA clone contained in the deposit.

[0743] Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions identified as "Start" and "End" in columns 7 and 8 as defined for SEQ ID NO:X in Table 1.

[0744] Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 150 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, and/or the cDNA in the related cDNA clone contained in the deposit.

[0745] Further preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 500 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, and/or the cDNA in the related cDNA clone contained in the deposit.

[0746] A further preferred embodiment is a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the nucleotide sequence of SEQ ID

NO:X in the range of positions identified as "Start" and "End" in columns 7 and 8 as defined for SEQ ID NO:X in Table 1.

[0747] A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, and/or the cDNA in the related cDNA clone contained in the deposit.

[0748] Also preferred is an isolated nucleic acid molecule which hybridizes under stringent hybridization conditions to a nucleic acid molecule comprising a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, and/or the cDNA in the related cDNA clone contained in the deposit, wherein said nucleic acid molecule which hybridizes does not hybridize under stringent hybridization conditions to a nucleic acid molecule having a nucleotide sequence consisting of only A residues or of only T residues.

[0749] Also preferred is a composition of matter comprising a DNA molecule which comprises a cDNA clone contained in the deposit.

[0750] Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in the nucleotide sequence of the cDNA in the related cDNA clone contained in the deposit.

[0751] Also preferred is an isolated nucleic acid molecule, wherein said sequence of at least 50 contiguous nucleotides is included in the nucleotide sequence of an open reading frame sequence encoded by the cDNA in the related cDNA clone contained in the deposit.

[0752] Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 150 contiguous nucleotides in the nucleotide sequence encoded by the cDNA in the related cDNA clone contained in the deposit.

[0753] A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 500 contiguous nucleotides in the nucleotide sequence encoded by the cDNA in the related cDNA clone contained in the deposit.

[0754] A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence encoded by the cDNA in the related cDNA clone contained in the deposit.

[0755] A further preferred embodiment is a method for detecting in a biological sample a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; and a nucleotide sequence encoded by the cDNA in the related cDNA clone contained in the deposit; which method comprises a step of comparing a nucleotide sequence of at least one nucleic acid molecule in said sample with a sequence selected from said group and determining whether the sequence of said nucleic acid molecule in said sample is at least 95% identical to said selected sequence.

[0756] Also preferred is the above method wherein said step of comparing sequences comprises determining the extent of nucleic acid hybridization between nucleic acid molecules in said sample and a nucleic acid molecule comprising said sequence selected from said group. Similarly, also preferred is the above method wherein said step of comparing sequences is performed by comparing the nucleotide sequence determined from a nucleic acid molecule in said sample with said sequence selected from said group. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

[0757] A further preferred embodiment is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting nucleic acid molecules in said sample, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; and a nucleotide sequence encoded by the cDNA in the related cDNA clone contained in the deposit.

[0758] Also preferred is the above method for identifying the species, tissue or cell type of a biological sample which comprises a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

[0759] Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a nucleotide sequence of SEQ ID NO:X; or the cDNA in the related cDNA clone identified in Table 1 which encodes a protein, wherein the method comprises a step of detecting in a biological sample obtained from said subject nucleic acid molecules, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; and a nucleotide sequence of the cDNA in the related cDNA clone contained in the deposit.

[0760] Also preferred is the above method for diagnosing a pathological condition which comprises a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

[0761] Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; and a nucleotide sequence encoded by the cDNA in the related cDNA clone contained in the deposit. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

[0762] Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise a DNA microarray or "chip" of at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 100, 150, 200, 250, 300, 500, 1000, 2000, 3000 or 4000 nucleotide sequences, wherein at least one sequence in said DNA microarray or "chip" is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; and a nucleotide sequence encoded by the cDNA in the cDNA clone referenced in Table 1. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

[0763] Also preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and/or a polypeptide encoded by the cDNA in the related cDNA clone contained in the deposit.

[0764] Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and/or a polypeptide encoded by the cDNA in the related cDNA clone contained in the deposit.

[0765] Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and/or a polypeptide encoded by the cDNA in the related cDNA clone contained in the deposit.

[0766] Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the complete amino acid sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and/or a polypeptide encoded by the cDNA in the related cDNA clone contained in the deposit.

[0767] Further preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the complete amino acid sequence of a polypeptide encoded by the cDNA clone referenced in Table 1.

[0768] Also preferred is a polypeptide wherein said sequence of contiguous amino acids is included in the amino acid sequence of a portion of said polypeptide encoded by the cDNA clone referenced in Table 1; a polypeptide encoded by SEQ ID NO:X; and/or the polypeptide sequence of SEQ ID NO:Y.

[0769] Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of a polypeptide encoded by the cDNA clone referenced in Table 1.

[0770] Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of a polypeptide encoded by the cDNA clone referenced in Table 1.

[0771] Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the amino acid sequence of a polypeptide encoded by the cDNA clone referenced in Table 1.

[0772] Further preferred is an isolated antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: a polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone contained in the deposit.

[0773] Further preferred is a method for detecting in a biological sample a polypeptide comprising an amino acid sequence which is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: a polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone referenced in Table 1; which method comprises a step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group and determining whether the sequence of said polypeptide molecule in said sample is at least 90% identical to said sequence of at least 10 contiguous amino acids.

[0774] Also preferred is the above method wherein said step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group comprises determining the extent of specific binding of polypeptides in said sample to an antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: a polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone referenced in Table 1.

[0775] Also preferred is the above method wherein said step of comparing sequences is performed by comparing the amino acid sequence determined from a polypeptide molecule in said sample with said sequence selected from said group.

[0776] Also preferred is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting polypeptide molecules in said sample, if any, comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone referenced in Table 1.

[0777] Also preferred is the above method for identifying the species, tissue or cell type of a biological sample, which method comprises a step of detecting polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the above group.

[0778] Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a nucleic acid sequence identified in Table 1 encoding a polypeptide, which method comprises a step of detecting in a biological sample obtained from said subject polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone referenced in Table 1.

[0779] In any of these methods, the step of detecting said polypeptide molecules includes using an antibody.

[0780] Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a nucleotide sequence encoding a polypeptide wherein said polypeptide comprises an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID

NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone referenced in Table 1.

[0781] Also preferred is an isolated nucleic acid molecule, wherein said nucleotide sequence encoding a polypeptide has been optimized for expression of said polypeptide in a prokaryotic host.

[0782] Also preferred is an isolated nucleic acid molecule, wherein said polypeptide comprises an amino acid sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone referenced in Table 1.

[0783] Further preferred is a method of making a recombinant vector comprising inserting any of the above isolated nucleic acid molecule into a vector. Also preferred is the recombinant vector produced by this method. Also preferred is a method of making a recombinant host cell comprising introducing the vector into a host cell, as well as the recombinant host cell produced by this method.

[0784] Also preferred is a method of making an isolated polypeptide comprising culturing this recombinant host cell under conditions such that said polypeptide is expressed and recovering said polypeptide. Also preferred is this method of making an isolated polypeptide, wherein said recombinant host cell is a eukaryotic cell and said polypeptide is a human protein comprising an amino acid sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone referenced in Table 1. The isolated polypeptide produced by this method is also preferred.

[0785] Also preferred is a method of treatment of an individual in need of an increased level of a protein activity, which method comprises administering to such an individual a Therapeutic comprising an amount of an isolated polypeptide, polynucleotide, immunogenic fragment or analogue thereof, binding agent, antibody, or antigen binding fragment of the claimed invention effective to increase the level of said protein activity in said individual.

[0786] Also preferred is a method of treatment of an individual in need of a decreased level of a protein activity, which method comprised administering to such an individual a Therapeutic comprising an amount of an isolated polypeptide, polynucleotide, immunogenic fragment or analogue thereof, binding agent, antibody, or antigen binding

fragment of the claimed invention effective to decrease the level of said protein activity in said individual.

[0787] Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as limiting.

Examples

Example 1: Isolation of a Selected cDNA Clone From the Deposited Sample

[0788] Each deposited cDNA clone is contained in a plasmid vector. Table 5 identifies the vectors used to construct the cDNA library from which each clone was isolated. In many cases, the vector used to construct the library is a phage vector from which a plasmid has been excised. The following correlates the related plasmid for each phage vector used in constructing the cDNA library. For example, where a particular clone is identified in Table 5 as being isolated in the vector "Lambda Zap," the corresponding deposited clone is in "pBluescript."

Vector Used to Construct Library	Corresponding Deposited Plasmid
Lambda Zap	pBluescript (pBS)
Uni-Zap XR	pBluescript (pBS)
Zap Express	pBK
lafmid BA	plafmid BA
pSport1	pSport1
pCMVSport 2.0	pCMVSport 2.0
pCMVSport 3.0	pCMVSport 3.0
pCR®2.1	pCR®2.1

[0789] Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., Nucleic Acids Res. 16:7583-7600 (1988); Alting-Mees, M. A. and Short, J. M., Nucleic Acids Res. 17:9494 (1989)) and pBK (Alting-Mees, M. A. et al., Strategies 5:58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Both can be transformed into E. coli strain XL-1 Blue, also available from Stratagene. pBS comes in 4 forms SK+, SK-, KS+ and KS. The S and K refers to the orientation of the polylinker to the T7 and T3 primer sequences which flank the polylinker region ("S" is for SacI and "K" is for KpnI which are the first sites on each respective end of the linker). "+" or "-" refer to the orientation of the f1 origin of replication ("ori"), such that in one

orientation, single stranded rescue initiated from the f1 ori generates sense strand DNA and in the other, antisense.

[0790] Vectors pSport1, pCMVSport 2.0 and pCMVSport 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into E. coli strain DH10B, also available from Life Technologies. (See, for instance, Gruber, C. E., et al., Focus 15:59 (1993).) Vector lafmid BA (Bento Soares, Columbia University, NY) contains an ampicillin resistance gene and can be transformed into E. coli strain XL-1 Blue. Vector pCR®2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into E. coli strain DH10B, available from Life Technologies. (See, for instance, Clark, J. M., Nuc. Acids Res. 16:9677-9686 (1988) and Mead, D. et al., Bio/Technology 9: (1991).) Preferably, a polynucleotide of the present invention does not comprise the phage vector sequences identified for the particular clone in Table 5, as well as the corresponding plasmid vector sequences designated above.

[0791] The deposited material in the sample assigned the ATCC Deposit Number cited by reference to Table 2 and 5 for any given cDNA clone also may contain one or more additional plasmids, each comprising a cDNA clone different from that given clone. Thus, deposits sharing the same ATCC Deposit Number contain at least a plasmid for each cDNA clone referenced in Table 1.

TABLE 5

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HUKA HUKB HUKC HUKD HUKE HUKF HUKG	Human Uterine Cancer	Lambda ZAP II	LP01
HCNA HCNB	Human Colon	Lambda Zap II	LP01
HFFA	Human Fetal Brain, random primed	Lambda Zap II	LP01
HTWA	Resting T-Cell	Lambda ZAP II	LP01
HBQA	Early Stage Human Brain, random primed	Lambda ZAP II	LP01
HLMB HLMF HLMG HLMH HLMI HLMJ HLMM HLMN	breast lymph node CDNA library	Lambda ZAP II	LP01
HCQA HCQB	human colon cancer	Lamda ZAP II	LP01
HMEA HMEC HMED HMEE HMEF HMEG HMEI HMEJ HMEK HMEL	Human Microvascular Endothelial Cells, fract. A	Lambda ZAP II	LP01
HUSA HUSC	Human Umbilical Vein Endothelial Cells, fract. A	Lambda ZAP II	LP01
HLQA HLQB	Hepatocellular Tumor	Lambda ZAP II	LP01
HHGA HHGB HHGC HHGD	Hemangiopericytoma	Lambda ZAP II	LP01
HSDM	Human Striatum Depression, re-rescue	Lambda ZAP II	LP01
HUSH	H Umbilical Vein Endothelial Cells, frac A, re-excision	Lambda ZAP II	LP01
HSGS	Salivary gland, subtracted	Lambda ZAP II	LP01
HFXA HFXB HFXC HFXD HFXE HFXF HFXG HFXH	Brain frontal cortex	Lambda ZAP II	LP01
HPQA HPQB HPQC	PERM TF274	Lambda ZAP II	LP01
HFXJ HFXK	Brain Frontal Cortex, re-excision	Lambda ZAP II	LP01
HCWA HCWB HCWC HCWD HCWE HCWF HCWG HCWH HCWI HCWJ HCWK	CD34 positive cells (Cord Blood)	ZAP Express	LP02
HCUA HCUB HCUC	CD34 depleted Buffy Coat (Cord Blood)	ZAP Express	LP02
HRSM	A-14 cell line	ZAP Express	LP02
HRSA	A1-CELL LINE	ZAP Express	LP02
HCUD HCUE HCUF HCUG HCUH HCUI	CD34 depleted Buffy Coat (Cord Blood), re-excision	ZAP Express	LP02
HBXE HBXF HBXG	H. Whole Brain #2, re-excision	ZAP Express	LP02
HRLM	L8 cell line	ZAP Express	LP02
HBXA HBXB HBXC HBXD	Human Whole Brain #2 - Oligo dT > 1.5Kb	ZAP Express	LP02
HUDA HUDB HUDC	Testes	ZAP Express	LP02
HHTM HHTN HHTO	H. hypothalamus, frac A;re-excision	ZAP Express	LP02
HHTL	H. hypothalamus, frac A	ZAP Express	LP02
HASA HASD	Human Adult Spleen	Uni-ZAP XR	LP03
HFKC HFKD HFKE HFKF HFKG	Human Fetal Kidney	Uni-ZAP XR	LP03
HE8A HE8B HE8C HE8D HE8E HE8F HE8M HE8N	Human 8 Week Whole Embryo	Uni-ZAP XR	LP03
HGBA HGBD HGBE HGBF HGBG HGBH HGBI	Human Gall Bladder	Uni-ZAP XR	LP03
HLHA HLHB HLHC HLHD HLHE HLHF HLHG HLHH HLHQ	Human Fetal Lung III	Uni-ZAP XR	LP03
HPMA HPMB HPMC HPMD HPME HPMF HPMG HPMH	Human Placenta	Uni-ZAP XR	LP03

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HPRA HPRB HPRC HPRD	Human Prostate	Uni-ZAP XR	LP03
HSIA HSIC HSID HSIE	Human Adult Small Intestine	Uni-ZAP XR	LP03
HTEA HTEB HTEC HTED HTEE HTEF HTEG HTEH HTEI HTEJ HTEK	Human Testes	Uni-ZAP XR	LP03
HTPA HTPB HTPC HTPD HTPE	Human Pancreas Tumor	Uni-ZAP XR	LP03
HTTA HTTB HTTC HTTD HTTE HTTF	Human Testes Tumor	Uni-ZAP XR	LP03
HAPA HAPB HAPC HAPM	Human Adult Pulmonary	Uni-ZAP XR	LP03
HETA HETB HETC HETD HETE HETF HETG HETH HETI	Human Endometrial Tumor	Uni-ZAP XR	LP03
HHFB HHFC HHFD HHFE HHFF HHFG HHFH HHFI	Human Fetal Heart	Uni-ZAP XR	LP03
HHPB HHPC HHPD HHPE HHPF HHPG HHPH	Human Hippocampus	Uni-ZAP XR	LP03
HCE1 HCE2 HCE3 HCE4 HCE5 HCEB HCEC HCED HCEE HCEF HCEG	Human Cerebellum	Uni-ZAP XR	LP03
HUVB HUVC HUVD HUVE	Human Umbilical Vein, Endo. remake	Uni-ZAP XR	LP03
HSTA HSTB HSTC HSTD	Human Skin Tumor	Uni-ZAP XR	LP03
HTAA HTAB HTAC HTAD HTAE	Human Activated T-Cells	Uni-ZAP XR	LP03
HFEA HFEB HFEC	Human Fetal Epithelium (Skin)	Uni-ZAP XR	LP03
HJPA HJPB HJPC HJPD	HUMAN JURKAT MEMBRANE BOUND POLYSOMES	Uni-ZAP XR	LP03
HESA	Human epithelioid sarcoma	Uni-Zap XR	LP03
HLTA HLTB HLTC HLTD HLTE HLTF	Human T-Cell Lymphoma	Uni-ZAP XR	LP03
HFTA HFTB HFTC HFTD	Human Fetal Dura Mater	Uni-ZAP XR	LP03
HRDA HRDB HRDC HRDD HRDE HRDF	Human Rhabdomyosarcoma	Uni-ZAP XR	LP03
HCAA HCAB HCAC	Cem cells cyclohexamide treated	Uni-ZAP XR	LP03
HRGA HRGB HRGC HRGD	Raji Cells, cyclohexamide treated	Uni-ZAP XR	LP03
HSUA HSUB HSUC HSUM	Supt Cells, cyclohexamide treated	Uni-ZAP XR	LP03
HT4A HT4C HT4D	Activated T-Cells, 12 hrs.	Uni-ZAP XR	LP03
HE9A HE9B HE9C HE9D HE9E HE9F HE9G HE9H HE9M HE9N	Nine Week Old Early Stage Human	Uni-ZAP XR	LP03
HATA HATB HATC HATD HATE	Human Adrenal Gland Tumor	Uni-ZAP XR	LP03
HT5A	Activated T-Cells, 24 hrs.	Uni-ZAP XR	LP03
HFGA HFGM	Human Fetal Brain	Uni-ZAP XR	LP03
HNEA HNEB HNEC HNED HNEE	Human Neutrophil	Uni-ZAP XR	LP03
HBGB HBGD	Human Primary Breast Cancer	Uni-ZAP XR	LP03
HBNA HBNB	Human Normal Breast	Uni-ZAP XR	LP03
HCAS	Cem Cells, cyclohexamide treated, subtra	Uni-ZAP XR	LP03
HHPS	Human Hippocampus, subtracted	pBS	LP03
HKCS HKCU	Human Colon Cancer, subtracted	pBS	LP03
HRGS	Raji cells, cyclohexamide treated, subtracted	pBS	LP03
HSUT	Supt cells, cyclohexamide treated, differentially expressed	pBS	LP03
HT4S	Activated T-Cells, 12 hrs, subtracted	Uni-ZAP XR	LP03
HCDA HCDB HCDC HCDD HCDE	Human Chondrosarcoma	Uni-ZAP XR	LP03
HOAA HOAB HOAC	Human Osteosarcoma	Uni-ZAP XR	LP03
HTLA HTLB HTLC HTLD HTLE	Human adult testis, large inserts	Uni-ZAP XR	LP03

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HTLF			
HLMA HLMC HLMD	Breast Lymph node cDNA library	Uni-ZAP XR	LP03
H6EA H6EB H6EC	HL-60, PMA 4H	Uni-ZAP XR	LP03
HTXA HTXB HTXC HTXD HTXE HTXF HTXG HTXH	Activated T-Cell (12hs)/Thiouridine labelledEco	Uni-ZAP XR	LP03
HNFA HNFB HNFC HNFD HNFE HNFF HNFG HNFH HNFJ	Human Neutrophil, Activated	Uni-ZAP XR	LP03
HTOB HTOC	HUMAN TONSILS, FRACTION 2	Uni-ZAP XR	LP03
HMGB	Human OB MG63 control fraction I	Uni-ZAP XR	LP03
HOPB	Human OB HOS control fraction I	Uni-ZAP XR	LP03
HORB	Human OB HOS treated (10 nM E2) fraction I	Uni-ZAP XR	LP03
HSVA HSVB HSVC	Human Chronic Synovitis	Uni-ZAP XR	LP03
HROA	HUMAN STOMACH	Uni-ZAP XR	LP03
HBJA HBJB HBJC HBJD HBJE HBJF HBJG HBJH HBJI HBJJ HBJK	HUMAN B CELL LYMPHOMA	Uni-ZAP XR	LP03
HCRA HCRB HCRC	human corpus colosum	Uni-ZAP XR	LP03
HODA HODB HODC HODD	human ovarian cancer	Uni-ZAP XR	LP03
HDSA	Dermatofibrosarcoma Protuberance	Uni-ZAP XR	LP03
HMWA HMWB HMWC HMWD HMWE HMWF HMWG HMWH HMWI HMWJ	Bone Marrow Cell Line (RS4;11)	Uni-ZAP XR	LP03
HSOA	stomach cancer (human)	Uni-ZAP XR	LP03
HERA	SKIN	Uni-ZAP XR	LP03
HMDA	Brain-medulloblastoma	Uni-ZAP XR	LP03
HGLA HGLB HGLD	Glioblastoma	Uni-ZAP XR	LP03
HEAA	H. Atrophic Endometrium	Uni-ZAP XR	LP03
HBCA HBCB	H. Lymph node breast Cancer	Uni-ZAP XR	LP03
HPWT	Human Prostate BPH, re-excision	Uni-ZAP XR	LP03
HFVG HFVH HFVI	Fetal Liver, subtraction II	pBS	LP03
HNFI	Human Neutrophils, Activated, re-excision	pBS	LP03
HBMB HBMC HBMD	Human Bone Marrow, re-excision	pBS	LP03
HKML HKMM HKMN	H. Kidney Medulla, re-excision	pBS	LP03
HKIX HKIY	H. Kidney Cortex, subtracted	pBS	LP03
HADT	H. Amygdala Depression, subtracted	pBS	LP03
H6AS	Hl-60, untreated, subtracted	Uni-ZAP XR	LP03
H6ES	HL-60, PMA 4H, subtracted	Uni-ZAP XR	LP03
H6BS	HL-60, RA 4h, Subtracted	Uni-ZAP XR	LP03
H6CS	HL-60, PMA 1d, subtracted	Uni-ZAP XR	LP03
HTXJ HTXK	Activated T-cell(12h)/Thiouridine-re-excision	Uni-ZAP XR	LP03
HMSA HMSB HMSC HMSD HMSE HMSF HMSG HMSH HMSI HMSJ HMSK	Monocyte activated	Uni-ZAP XR	LP03
HAGA HAGB HAGC HAGD HAGE HAGF	Human Amygdala	Uni-ZAP XR	LP03
HSRA HSRB HSRE	STROMAL -OSTEOCLASTOMA	Uni-ZAP XR	LP03
HSRD HSRF HSRG HSRH	Human Osteoclastoma Stromal Cells - unamplified	Uni-ZAP XR	LP03
HSQA HSQB HSQC HSQD HSQE	Stromal cell TF274	Uni-ZAP XR	LP03

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HSQF HSQG			
HSKA HSKB HSKC HSKD HSKE HSKF HSKZ	Smooth muscle, serum treated	Uni-ZAP XR	LP03
HSLA HSLB HSLC HSLD HSLE HSLF HSLG	Smooth muscle,control	Uni-ZAP XR	LP03
HSDA HSDD HSDE HSDF HSDG HSDH	Spinal cord	Uni-ZAP XR	LP03
HPWS	Prostate-BPH subtracted II	pBS	LP03
HSKW HSKX HSKY	Smooth Muscle- HASTE normalized	pBS	LP03
HFPB HFPC HFPD	H. Frontal cortex,epileptic;re-excision	Uni-ZAP XR	LP03
HSDI HSDJ HSDK	Spinal Cord, re-excision	Uni-ZAP XR	LP03
HSKN HSKO	Smooth Muscle Serum Treated, Norm	pBS	LP03
HSKG HSKH HSKI	Smooth muscle, serum induced,re-exc	pBS	LP03
HFCA HFCB HFCC HFCD HFCE HFCF	Human Fetal Brain	Uni-ZAP XR	LP04
HPTA HPTB HPTD	Human Pituitary	Uni-ZAP XR	LP04
HTHB HTHC HTHD	Human Thymus	Uni-ZAP XR	LP04
HE6B HE6C HE6D HE6E HE6F HE6G HE6S	Human Whole Six Week Old Embryo	Uni-ZAP XR	LP04
HSSA HSSB HSSC HSSD HSSE HSSF HSSG HSSH HSSI HSSJ HSSK	Human Synovial Sarcoma	Uni-ZAP XR	LP04
HE7T	7 Week Old Early Stage Human, subtracted	Uni-ZAP XR	LP04
HEPA HEPB HEPC	Human Epididymus	Uni-ZAP XR	LP04
HSNA HSNB HSNC HSNM HSNN	Human Synovium	Uni-ZAP XR	LP04
HPFB HPFC HPFD HPFE	Human Prostate Cancer, Stage C fraction	Uni-ZAP XR	LP04
HE2A HE2D HE2E HE2H HE2I HE2M HE2N HE2O	12 Week Old Early Stage Human	Uni-ZAP XR	LP04
HE2B HE2C HE2F HE2G HE2P HE2Q	12 Week Old Early Stage Human, II	Uni-ZAP XR	LP04
HPTS HPTT HPTU	Human Pituitary, subtracted	Uni-ZAP XR	LP04
HAUA HAUB HAUC	Amniotic Cells - TNF induced	Uni-ZAP XR	LP04
HAQA HAQB HAQC HAQD	Amniotic Cells - Primary Culture	Uni-ZAP XR	LP04
HWTA HWTB HWTC	wilm's tumor	Uni-ZAP XR	LP04
HBSD	Bone Cancer, re-excision	Uni-ZAP XR	LP04
HSGB	Salivary gland, re-excision	Uni-ZAP XR	LP04
HSJA HSJB HSJC	Smooth muscle-ILb induced	Uni-ZAP XR	LP04
HSXA HSXB HSXC HSXD	Human Substantia Nigra	Uni-ZAP XR	LP04
HSHA HSHB HSHC	Smooth muscle, IL1b induced	Uni-ZAP XR	LP04
HOUA HOUB HOUC HOUD HOUE	Adipocytes	Uni-ZAP XR	LP04
HPWA HPWB HPWC HPWD HPWE	Prostate BPH	Uni-ZAP XR	LP04
HELA HELB HELC HELD HELE HELF HELG HELH	Endothelial cells-control	Uni-ZAP XR	LP04
HEMA HEMB HEMC HEMD HEME HEMF HEMG HEMH	Endothelial-induced	Uni-ZAP XR	LP04
HBIA HBIB HBIC	Human Brain, Striatum	Uni-ZAP XR	LP04
HHSA HHSB HHSC HHSD HHSE	Human Hypothalmus,Schizophrenia	Uni-ZAP XR	LP04
HNGA HNGB HNGC HNGD HNGE HNGF HNGG HNGH HNGI HNGJ	neutrophils control	Uni-ZAP XR	LP04
HNHA HNHB HNHC HNHD HNHE HNHF HNHG HNHH HNHI HNHJ	Neutrophils IL-1 and LPS induced	Uni-ZAP XR	LP04
HSDB HSDC	STRIATUM DEPRESSION	Uni-ZAP XR	LP04

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HHPT	Hypothalamus	Uni-ZAP XR	LP04
HSAT HSAU HSAV HSAW HSAX HSAY HSAZ	Anergic T-cell	Uni-ZAP XR	LP04
HBMS HBMT HBMU HBMV HBMW HBMX	Bone marrow	Uni-ZAP XR	LP04
HOEA HOEB HOEC HOED HOEE HOEF HOEJ	Osteoblasts	Uni-ZAP XR	LP04
HAIA HAIB HAIC HAID HAIE HAIF	Epithelial-TNFa and INF induced	Uni-ZAP XR	LP04
HTGA HTGB HTGC HTGD	Apoptotic T-cell	Uni-ZAP XR	LP04
HMCA HMCB HMCC HMCD HMCE	Macrophage-oxLDL	Uni-ZAP XR	LP04
HMAA HMAB HMAC HMAD HMAE HMAF HMAG	Macrophage (GM-CSF treated)	Uni-ZAP XR	LP04
HPHA	Normal Prostate	Uni-ZAP XR	LP04
HPIA HPIB HPIC	LNCAP prostate cell line	Uni-ZAP XR	LP04
HPJA HPJB HPJC	PC3 Prostate cell line	Uni-ZAP XR	LP04
HOSE HOSF HOSG	Human Osteoclastoma, re-excision	Uni-ZAP XR	LP04
HTGE HTGF	Apoptotic T-cell, re-excision	Uni-ZAP XR	LP04
HMAJ HMAK	H Macrophage (GM-CSF treated), re-excision	Uni-ZAP XR	LP04
HACB HACC HACD	Human Adipose Tissue, re-excision	Uni-ZAP XR	LP04
HFPA	H. Frontal Cortex, Epileptic	Uni-ZAP XR	LP04
HFAA HFAB HFAC HFAD HFAE	Alzheimers, spongy change	Uni-ZAP XR	LP04
HFAM	Frontal Lobe, Dementia	Uni-ZAP XR	LP04
HMIA HMIB HMIC	Human Manic Depression Tissue	Uni-ZAP XR	LP04
HTSA HTSE HTSF HTSG HTSH	Human Thymus	pBS	LP05
HPBA HPBB HPBC HPBD HPBE	Human Pineal Gland	pBS	LP05
HSAA HSAB HSAC	HSA 172 Cells	pBS	LP05
HSBA HSBB HSBC HSBM	HSC172 cells	pBS	LP05
HJAA HJAB HJAC HJAD	Jurkat T-cell G1 phase	pBS	LP05
HJBA HJBB HJBC HJBD	Jurkat T-Cell, S phase	pBS	LP05
HAFA HAFB	Aorta endothelial cells + TNF-a	pBS	LP05
HAWA HAWB HAWC	Human White Adipose	pBS	LP05
HTNA HTNB	Human Thyroid	pBS	LP05
HONA	Normal Ovary, Premenopausal	pBS	LP05
HARA HARB	Human Adult Retina	pBS	LP05
HLJA HLJB	Human Lung	pCMVSport 1	LP06
HOFM HOFN HOFO	H. Ovarian Tumor, II, OV5232	pCMVSport 2.0	LP07
HOGA HOGB HOGC	OV 10-3-95	pCMVSport 2.0	LP07
HCGL	CD34+cells, II	pCMVSport 2.0	LP07
HDLA	Hodgkin's Lymphoma I	pCMVSport 2.0	LP07
HDTA HDTB HDTC HDTD HDTE	Hodgkin's Lymphoma II	pCMVSport 2.0	LP07
HKAA HKAB HKAC HKAD HKAE HKAF HKAG HKAH	Keratinocyte	pCMVSport2.0	LP07
HCIM	CAPFINDER, Crohn's Disease, lib 2	pCMVSport 2.0	LP07
HKAL	Keratinocyte, lib 2	pCMVSport2.0	LP07
HKAT	Keratinocyte, lib 3	pCMVSport2.0	LP07
HNDA	Nasal polyps	pCMVSport2.0	LP07
HDRA	H. Primary Dendritic Cells,lib 3	pCMVSport2.0	LP07

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HOHA HOHB HOHC	Human Osteoblasts II	pCMVSport2.0	LP07
HLDA HLDB HLDC	Liver, Hepatoma	pCMVSport3.0	LP08
HLDN HLDO HLDP	Human Liver, normal	pCMVSport3.0	LP08
HMTA	pBMC stimulated w/ poly I/C	pCMVSport3.0	LP08
HNTA	NTERA2, control	pCMVSport3.0	LP08
HDPA HDPB HDPC HDPD HDPF HDPG HDPH HDPI HDPJ HDPK	Primary Dendritic Cells, lib 1	pCMVSport3.0	LP08
HDPM HDPN HDPO HDPP	Primary Dendritic cells,frac 2	pCMVSport3.0	LP08
HMUA HMUB HMUC	Myoloid Progenitor Cell Line	pCMVSport3.0	LP08
HHEA HHEB HHEC HHED	T Cell helper I	pCMVSport3.0	LP08
HHEM HHEN HHEO HHEP	T cell helper II	pCMVSport3.0	LP08
HEQA HEQB HEQC	Human endometrial stromal cells	pCMVSport3.0	LP08
HJMA HJMB	Human endometrial stromal cells-treated with progesterone	pCMVSport3.0	LP08
HSWA HSWB HSWC	Human endometrial stromal cells-treated with estradiol	pCMVSport3.0	LP08
HSYA HSYB HSYC	Human Thymus Stromal Cells	pCMVSport3.0	LP08
HLWA HLWB HLWC	Human Placenta	pCMVSport3.0	LP08
HRAA HRAB HRAC	Rejected Kidney, lib 4	pCMVSport3.0	LP08
HMTM	PCR, pBMC I/C treated	PCRII	LP09
HMJA	H. Meningima, M6	pSport 1	LP10
HMKA HMKB HMKC HMKD HMKE	H. Meningima, M1	pSport 1	LP10
HUSG HUSI	Human umbilical vein endothelial cells, IL-4 induced	pSport 1	LP10
HUSX HUSY	Human Umbilical Vein Endothelial Cells, uninduced	pSport 1	LP10
HOFA	Ovarian Tumor I, OV5232	pSport 1	LP10
HCFA HCFB HCFC HCFD	T-Cell PHA 16 hrs	pSport 1	LP10
HCFL HCFM HCFN HCFO	T-Cell PHA 24 hrs	pSport 1	LP10
HADA HADC HADD HADE HADF HADG	Human Adipose	pSport 1	LP10
HOVA HOVB HOVC	Human Ovary	pSport 1	LP10
HTWB HTWC HTWD HTWE HTWF	Resting T-Cell Library,II	pSport 1	LP10
HMMA	Spleen metastic melanoma	pSport 1	LP10
HLYA HLYB HLYC HLYD HLYE	Spleen, Chronic lymphocytic leukemia	pSport 1	LP10
HCGA	CD34+ cell, I	pSport 1	LP10
HEOM HEON	Human Eosinophils	pSport 1	LP10
HTDA	Human Tonsil, Lib 3	pSport 1	LP10
HSPA	Salivary Gland, Lib 2	pSport 1	LP10
HCHA HCHB HCHC	Breast Cancer cell line, MDA 36	pSport 1	LP10
HCHM HCHN	Breast Cancer Cell line, angiogenic	pSport 1	LP10
HCIA	Crohn's Disease	pSport 1	LP10
HDAA HDAB HDAC	HEL cell line	pSport 1	LP10
HABA	Human Astrocyte	pSport 1	LP10
HUFA HUFB HUFC	Ulcerative Colitis	pSport 1	LP10
HNTM	NTERA2 + retinoic acid, 14 days	pSport 1	LP10
HDQA	Primary Dendritic cells,CapFinder2, frac 1	pSport 1	LP10
HDQM	Primary Dendritic Cells, CapFinder, frac	pSport 1	LP10

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
	2		
HLDX	Human Liver, normal,CapFinder	pSport 1	LP10
HULA HULB HULC	Human Dermal Endothelial Cells,untreated	pSport1	LP10
HUMA	Human Dermal Endothelial cells,treated	pSport1	LP10
HCJA	Human Stromal Endometrial fibroblasts, untreated	pSport1	LP10
HCJM	Human Stromal endometrial fibroblasts, treated w/ estradiol	pSport1	LP10
HEDA	Human Stromal endometrial fibroblasts, treated with progesterone	pSport1	LP10
HFNA	Human ovary tumor cell OV350721	pSport1	LP10
HKGA HKGB HKGC HKGD	Merkel Cells	pSport1	LP10
HISA HISB HISC	Pancreas Islet Cell Tumor	pSport1	LP10
HLSA	Skin, burned	pSport1	LP10
HBZA	Prostate,BPH, Lib 2	pSport 1	LP10
HBZS	Prostate BPH,Lib 2, subtracted	pSport 1	LP10
HFIA HFIB HFIC	Synovial Fibroblasts (control)	pSport 1	LP10
HFIH HFII HFIJ	Synovial hypoxia	pSport 1	LP10
HFIT HFIU HFIV	Synovial IL-1/TNF stimulated	pSport 1	LP10
HGCA	Messangial cell, frac 1	pSport1	LP10
HMVA HMVB HMVC	Bone Marrow Stromal Cell, untreated	pSport1	LP10
HFIX HFIY HFIZ	Synovial Fibroblasts (Il1/TNF), subt	pSport1	LP10
HFOX HFOY HFOZ	Synovial hypoxia-RSF subtracted	pSport1	LP10
HMQA HMQB HMQC HMQD	Human Activated Monocytes	Uni-ZAP XR	LP11
HLIA HLIB HLIC	Human Liver	pCMVSport 1	LP012
HHBA HHBB HHBC HHBD HHBE	Human Heart	pCMVSport 1	LP012
HBBA HBBB	Human Brain	pCMVSport 1	LP012
HLJA HLJB HLJC HLJD HLJE	Human Lung	pCMVSport 1	LP012
HOGA HOGB HOGC	Ovarian Tumor	pCMVSport 2.0	LP012
HTJM	Human Tonsils, Lib 2	pCMVSport 2 0	LP012
HAMF HAMG	KMH2	pCMVSport 3.0	LP012
HAJA HAJB HAJC	L428	pCMVSport 3.0	LP012
HWBA HWBB HWBC HWBD HWBE	Dendritic cells, pooled	pCMVSport 3.0	LP012
HWAA HWAB HWAC HWAD HWAE	Human Bone Marrow, treated	pCMVSport 3.0	LP012
HYAA HYAB HYAC	B Cell lymphoma	pCMVSport 3.0	LP012
HWHG HWHH HWHI	Healing groin wound, 6.5 hours post incision	pCMVSport 3.0	LP012
HWHP HWHQ HWHR	Healing groin wound; 7.5 hours post incision	pCMVSport 3.0	LP012
HARM	Healing groin wound - zero hr post-incision (control)	pCMVSport 3.0	LP012
HBIM	Olfactory epithelium; nasalcavity	pCMVSport 3.0	LP012
HWDA	Healing Abdomen wound; 70&90 min post incision	pCMVSport 3.0	LP012
HWEA	Healing Abdomen Wound:15 days post incision	pCMVSport 3.0	LP012
HWJA	Healing Abdomen Wound:21&29 days	pCMVSport 3.0	LP012
HNAL	Human Tongue, frac 2	pSport1	LP012
HMJA	H. Meniingima, M6	pSport1	LP012
HMKA HMKB HMKC HMKD HMKE	H. Meningima, M1	pSport1	LP012

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HOFA	Ovarian Tumor I, OV5232	pSport1	LP012
HCFA HCFB HCFC HCFD	T-Cell PHA 16 hrs	pSport1	LP012
HCFL HCFM HCFN HCFO	T-Cell PHA 24 hrs	pSport1	LP012
HMMA HMMB HMMC	Spleen metastic melanoma	pSport1	LP012
HTDA	Human Tonsil, Lib 3	pSport1	LP012
HDBA	Human Fetal Thymus	pSport1	LP012
HDUA	Pericardium	pSport1	LP012
HBZA	Prostate,BPH, Lib 2	pSport1	LP012
HWCA	Larynx tumor	pSport1	LP012
HWKA	Normal lung	pSport1	LP012
HSMB	Bone marrow stroma,treated	pSport1	LP012
HBHM	Normal trachea	pSport1	LP012
HLFC	Human Larynx	pSport1	LP012
HLRB	Siebben Polyposis	pSport1	LP012
HNIA	Mammary Gland	pSport1	LP012
HNJB	Palate carcinoma	pSport1	LP012
HNKA	Palate normal	pSport1	LP012
HMZA	Pharynx carcinoma	pSport1	LP012
HABG	Cheek Carcinoma	pSport1	LP012
HMZM	Pharynx Carcinoma	pSport1	LP012
HDRM	Larynx Carcinoma	pSport1	LP012
HVAA	Pancreas normal PCA4 No	pSport1	LP012
HICA	Tongue carcinoma	pSport1	LP012
HUKA HUKB HUKC HUKD HUKE	Human Uterine Cancer	Lambda ZAP II	LP013
HFFA	Human Fetal Brain, random primed	Lambda ZAP II	LP013
HTUA	Activated T-cell labeled with 4-thioluri	Lambda ZAP II	LP013
HBQA	Early Stage Human Brain, random primed	Lambda ZAP II	LP013
HMEB	Human microvascular Endothelial cells, fract. B	Lambda ZAP II	LP013
HUSH	Human Umbilical Vein Endothelial cells, fract. A, re-excision	Lambda ZAP II	LP013
HLQC HLQD	Hepatocellular tumor, re-excision	Lambda ZAP II	LP013
HTWJ HTWK HTWL	Resting T-cell, re-excision	Lambda ZAP II	LP013
HF6S	Human Whole 6 week Old Embryo (II), subt	pBluescript	LP013
HHPS	Human Hippocampus, subtracted	pBluescript	LP013
HL1S	LNCAP, differential expression	pBluescript	LP013
HLHS HLHT	Early Stage Human Lung, Subtracted	pBluescript	LP013
HSUS	Supt cells, cyclohexamide treated, subtracted	pBluescript	LP013
HSUT	Supt cells, cyclohexamide treated, differentially expressed	pBluescript	LP013
HSDS	H. Striatum Depression, subtracted	pBluescript	LP013
HPTZ	Human Pituitary, Subtracted VII	pBluescript	LP013
HSDX	H. Striatum Depression, subt II	pBluescript	LP013
HSDZ	H. Striatum Depression, subt	pBluescript	LP013
HPBA HPBB HPBC HPBD HPBE	Human Pineal Gland	pBluescript SK-	LP013
HRTA	Colorectal Tumor	pBluescript SK-	LP013
HSBA HSBB HSBC HSBM	HSC172 cells	pBluescript SK-	LP013
HJAA HJAB HJAC HJAD	Jurkat T-cell G1 phase	pBluescript SK-	LP013
HJBA HJBB HJBC HJBD	Jurkat T-cell, S1 phase	pBluescript SK-	LP013

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HTNA HTNB	Human Thyroid	pBluescript SK-	LP013
HAHA HAHB	Human Adult Heart	Uni-ZAP XR	LP013
HE6A	Whole 6 week Old Embryo	Uni-ZAP XR	LP013
HFCA HFCB HFCC HFCD HFCE	Human Fetal Brain	Uni-ZAP XR	LP013
HFKC HFKD HFKE HFKF HFKG	Human Fetal Kidney	Uni-ZAP XR	LP013
HGBA HGBD HGBE HGBF HGBG	Human Gall Bladder	Uni-ZAP XR	LP013
HPRA HPRB HPRC HPRD	Human Prostate	Uni-ZAP XR	LP013
HTEA HTEB HTEC HTED HTEE	Human Testes	Uni-ZAP XR	LP013
HTTA HTTB HTTC HTTD HTTE	Human Testes Tumor	Uni-ZAP XR	LP013
HYBA HYBB	Human Fetal Bone	Uni-ZAP XR	LP013
HFLA	Human Fetal Liver	Uni-ZAP XR	LP013
HHFB HHFC HHFD HHFE HHFF	Human Fetal Heart	Uni-ZAP XR	LP013
HUVB HUVC HUVD HUVE	Human Umbilical Vein, End. remake	Uni-ZAP XR	LP013
HTHB HTHC HTHD	Human Thymus	Uni-ZAP XR	LP013
HSTA HSTB HSTC HSTD	Human Skin Tumor	Uni-ZAP XR	LP013
HTAA HTAB HTAC HTAD HTAE	Human Activated T-cells	Uni-ZAP XR	LP013
HFEA HFEB HFEC	Human Fetal Epithelium (skin)	Uni-ZAP XR	LP013
HJPA HJPB HJPC HJPD	Human Jurkat Membrane Bound Polysomes	Uni-ZAP XR	LP013
HESA	Human Epithelioid Sarcoma	Uni-ZAP XR	LP013
HALS	Human Adult Liver, Subtracted	Uni-ZAP XR	LP013
HFTA HFTB HFTC HFTD	Human Fetal Dura Mater	Uni-ZAP XR	LP013
HCAA HCAB HCAC	Cem cells, cyclohexamide treated	Uni-ZAP XR	LP013
HRGA HRGB HRGC HRGD	Raji Cells, cyclohexamide treated	Uni-ZAP XR	LP013
HE9A HE9B HE9C HE9D HE9E	Nine Week Old Early Stage Human	Uni-ZAP XR	LP013
HSFA	Human Fibrosarcoma	Uni-ZAP XR	LP013
HATA HATB HATC HATD HATE	Human Adrenal Gland Tumor	Uni-ZAP XR	LP013
HTRA	Human Trachea Tumor	Uni-ZAP XR	LP013
HE2A HE2D HE2E HE2H HE2I	12 Week Old Early Stage Human	Uni-ZAP XR	LP013
HE2B HE2C HE2F HE2G HE2P	12 Week Old Early Stage Human, II	Uni-ZAP XR	LP013
HNEA HNEB HNEC HNED HNEE	Human Neutrophil	Uni-ZAP XR	LP013
HBGA	Human Primary Breast Cancer	Uni-ZAP XR	LP013
HPTS HPTT HPTU	Human Pituitary, subtracted	Uni-ZAP XR	LP013
HMQA HMQB HMQC HMQD	Human Activated Monocytes	Uni-ZAP XR	LP013
HOAA HOAB HOAC	Human Osteosarcoma	Uni-ZAP XR	LP013
HTOA HTOD HTOE HTOF HTOG	human tonsils	Uni-ZAP XR	LP013
HMGB	Human OB MG63 control fraction I	Uni-ZAP XR	LP013
HOPB	Human OB HOS control fraction I	Uni-ZAP XR	LP013
HOQB	Human OB HOS treated (1 nM E2) fraction I	Uni-ZAP XR	LP013
HAUA HAUB HAUC	Amniotic Cells - TNF induced	Uni-ZAP XR	LP013
HAQA HAQB HAQC HAQD	Amniotic Cells - Primary Culture	Uni-ZAP XR	LP013
HROA HROC	HUMAN STOMACH	Uni-ZAP XR	LP013
HBJA HBJB HBJC HBJD HBJE	HUMAN B CELL LYMPHOMA	Uni-ZAP XR	LP013
HODA HODB HODC HODD	human ovarian cancer	Uni-ZAP XR	LP013
HCPA	Corpus Callosum	Uni-ZAP XR	LP013
HSOA	stomach cancer (human)	Uni-ZAP XR	LP013
HERA	SKIN	Uni-ZAP XR	LP013
HMDA	Brain-medulloblastoma	Uni-ZAP XR	LP013
HGLA HGLB HGLD	Glioblastoma	Uni-ZAP XR	LP013

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HWTA HWTB HWTC	wilm's tumor	Uni-ZAP XR	LP013
HEAA	H. Atrophic Endometrium	Uni-ZAP XR	LP013
HAPN HAPO HAPP HAPQ HAPR	Human Adult Pulmonary;re-excision	Uni-ZAP XR	LP013
HLTG HLTH	Human T-cell lymphoma;re-excision	Uni-ZAP XR	LP013
HAHC HAHD HAHE	Human Adult Heart;re-excision	Uni-ZAP XR	LP013
HAGA HAGB HAGC HAGD HAGE	Human Amygdala	Uni-ZAP XR	LP013
HSJA HSJB HSJC	Smooth muscle-ILb induced	Uni-ZAP XR	LP013
HSHA HSHB HSHC	Smooth muscle, IL1b induced	Uni-ZAP XR	LP013
HPWA HPWB HPWC HPWD HPWE	Prostate BPH	Uni-ZAP XR	LP013
HPIA HPIB HPIC	LNCAP prostate cell line	Uni-ZAP XR	LP013
HPJA HPJB HPJC	PC3 Prostate cell line	Uni-ZAP XR	LP013
HBTA	Bone Marrow Stroma, TNF&LPS ind	Uni-ZAP XR	LP013
HMCF HMCG HMCH HMCI HMCJ	Macrophage-oxLDL; re-excision	Uni-ZAP XR	LP013
HAGG HAGH HAGI	Human Amygdala;re-excision	Uni-ZAP XR	LP013
HACA	H. Adipose Tissue	Uni-ZAP XR	LP013
HKFB	K562 + PMA (36 hrs),re-excision	ZAP Express	LP013
HCWT HCWU HCWV	CD34 positive cells (cord blood),re-ex	ZAP Express	LP013
HBWA	Whole brain	ZAP Express	LP013
HBXA HBXB HBXC HBXD	Human Whole Brain #2 - Oligo dT > 1.5Kb	ZAP Express	LP013
HAVM	Temporal cortex-Alzheizmer	pT-Adv	LP014
HAVT	Hippocampus, Alzheimer Subtracted	pT-Adv	LP014
HHAS	CHME Cell Line	Uni-ZAP XR	LP014
HAJR	Larynx normal	pSport 1	LP014
HWLE HWLF HWLG HWLH	Colon Normal	pSport 1	LP014
HCRM HCRN HCRO	Colon Carcinoma	pSport 1	LP014
HWLI HWLJ HWLK	Colon Normal	pSport 1	LP014
HWLQ HWLR HWLS HWLT	Colon Tumor	pSport 1	LP014
HBFM	Gastrocnemius Muscle	pSport 1	LP014
HBOD HBOE	Quadriceps Muscle	pSport 1	LP014
HBKD HBKE	Soleus Muscle	pSport 1	LP014
HCCM	Pancreatic Langerhans	pSport 1	LP014
HWGA	Larynx carcinoma	pSport 1	LP014
HWGM HWGN	Larynx carcinoma	pSport 1	LP014
HWLA HWLB HWLC	Normal colon	pSport 1	LP014
HWLM HWLN	Colon Tumor	pSport 1	LP014
HVAM HVAN HVAO	Pancreas Tumor	pSport 1	LP014
HWGQ	Larynx carcinoma	pSport 1	LP014
HAQM HAQN	Salivary Gland	pSport 1	LP014
HASM	Stomach; normal	pSport 1	LP014
HBCM	Uterus; normal	pSport 1	LP014
HCDM	Testis; normal	pSport 1	LP014
HDJM	Brain; normal	pSport 1	LP014
HEFM	Adrenal Gland,normal	pSport 1	LP014
HBAA	Rectum normal	pSport 1	LP014
HFDM	Rectum tumour	pSport 1	LP014
HGAM	Colon, normal	pSport 1	LP014
HHMM	Colon, tumour	pSport 1	LP014
HCLB HCLC	Human Lung Cancer	Lambda Zap II	LP015
HRLA	L1 Cell line	ZAP Express	LP015

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
HHAM	Hypothalamus, Alzheimer's	pCMVSport 3.0	LP015
HKBA	Ku 812F Basophils Line	pSport 1	LP015
HS2S	Saos2, Dexamethosome Treated	pSport 1	LP016
HA5A	Lung Carcinoma A549 TNFalpha activated	pSport 1	LP016
HTFM	TF-1 Cell Line GM-CSF Treated	pSport 1	LP016
HYAS	Thyroid Tumour	pSport 1	LP016
HUTS	Larynx Normal	pSport 1	LP016
HXOA	Larynx Tumor	pSport 1	LP016
HEAH	Ea.hy.926 cell line	pSport 1	LP016
HINA	Adenocarcinoma Human	pSport 1	LP016
HRMA	Lung Mesothelium	pSport 1	LP016
HLCL	Human Pre-Differentiated Adipocytes	Uni-Zap XR	LP017
HS2A	Saos2 Cells	pSport 1	LP020
HS2I	Saos2 Cells; Vitamin D3 Treated	pSport 1	LP020
HUCM	CHME Cell Line, untreated	pSport 1	LP020
HEPN	Aryepiglottis Normal	pSport 1	LP020
HPSN	Sinus Piniformis Tumour	pSport 1	LP020
HNSA	Stomach Normal	pSport 1	LP020
HNSM	Stomach Tumour	pSport 1	LP020
HNLA	Liver Normal Met5No	pSport 1	LP020
HUTA	Liver Tumour Met 5 Tu	pSport 1	LP020
HOCN	Colon Normal	pSport 1	LP020
HOCT	Colon Tumor	pSport 1	LP020
HTNT	Tongue Tumour	pSport 1	LP020
HLXN	Larynx Normal	pSport 1	LP020
HLXT	Larynx Tumour	pSport 1	LP020
HTYN	Thymus	pSport 1	LP020
HPLN	Placenta	pSport 1	LP020
HTNG	Tongue Normal	pSport 1	LP020
HZAA	Thyroid Normal (SDCA2 No)	pSport 1	LP020
HWES	Thyroid Thyroiditis	pSport 1	LP020
HFHD	Ficolled Human Stromal Cells, 5Fu treated	pTrip1Ex2	LP021
HFHM,HFHN	Ficolled Human Stromal Cells, Untreated	pTrip1Ex2	LP021
HPCI	Hep G2 Cells, lambda library	lambda Zap-CMV XR	LP021
HBCA,HBCB,HBCC	H. Lymph node breast Cancer	Uni-ZAP XR	LP021
HCOK	Chondrocytes	pSPORT1	LP022
HDCA, HDCB, HDCC	Dendritic Cells From CD34 Cells	pSPORT1	LP022
HDMA, HDMB	CD40 activated monocyte dendritic cells	pSPORT1	LP022
HDDM, HDDN, HDDO	LPS activated derived dendritic cells	pSPORT1	LP022
HPCR	Hep G2 Cells, PCR library	lambda Zap-CMV XR	LP022
HAAA, HAAB, HAAC	Lung, Cancer (4005313A3): Invasive Poorly Differentiated Lung Adenocarcinoma	pSPORT1	LP022
HIPA, HIPB, HIPC	Lung, Cancer (4005163 B7): Invasive, Poorly Diff. Adenocarcinoma, Metastatic	pSPORT1	LP022
HOOH, HOOI	Ovary, Cancer: (4004562 B6) Papillary Serous Cystic Neoplasm, Low	pSPORT1	LP022

Libraries owned by Catalog	Catalog Description	Vector	ATCC Deposit
	Malignant Pot		
HIDA	Lung, Normal: (4005313 B1)	pSPORT1	LP022
HUJA,HUJB,HUJC,HUJD.HUJE	B-Cells	pCMVSport 3.0	LP022
HNOA,HNOB,HNOC,HNOD	Ovary, Normal: (9805C040R)	pSPORT1	LP022
HNLM	Lung, Normal: (4005313 B1)	pSPORT1	LP022
HSCL	Stromal Cells	pSPORT1	LP022
HAAX	Lung, Cancer: (4005313 A3) Invasive Poorly-differentiated Metastatic lung adenocarcinoma	pSPORT1	LP022
HUUA,HUUB,HUUC,HUUD	B-cells (unstimulated)	pTrip1Ex2	LP022
HWWA,HWWB,HWWC,HWWD,HWWE,HWWF,HWWG	B-cells (stimulated)	pSPORT1	LP022
HCCC	Colon, Cancer: (9808C064R)	pCMVSport 3.0	LP023
HPDO HPDP HPDQ HPDR HPD	Ovary, Cancer (9809C332): Poorly differentiated adenocarcinoma	pSport 1	LP023
HPCO HPCP HPCQ HPCT	Ovary, Cancer (15395A1F): Grade II Papillary Carcinoma	pSport 1	LP023
HOCM HOCO HOCP HOCQ	Ovary, Cancer: (15799A1F) Poorly differentiated carcinoma	pSport 1	LP023
HCBM HCBN HCBO	Breast, Cancer: (4004943 A5)	pSport 1	LP023
HNBT HNBU HNBV	Breast, Normal: (4005522B2)	pSport 1	LP023
HBCP HBCQ	Breast, Cancer: (4005522 A2)	pSport 1	LP023
HBCJ	Breast, Cancer: (9806C012R)	pSport 1	LP023
HSAM HSAN	Stromal cells 3.88	pSport 1	LP023
HVCA HVCB HVCC HVCD	Ovary, Cancer: (4004332 A2)	pSport 1	LP023
HSCK HSEN HSEO	Stromal cells (HBM3.18)	pSport 1	LP023
HSCP HSCQ	stromal cell clone 2.5	pSport 1	LP023
HUXA	Breast Cancer: (4005385 A2)	pSport 1	LP023
HCOM HCON HCOO HCOP HCOQ	Ovary, Cancer (4004650 A3): Well-Differentiated Micropapillary Serous Carcinoma	pSport 1	LP023
HBNM	Breast, Cancer: (9802C020E)	pSport 1	LP023
HVVA HVVB HVVC HVVD HVVE	Human Bone Marrow, treated	pSport 1	LP023

[0792] Two approaches can be used to isolate a particular clone from the deposited sample of plasmid DNAs cited for that clone in Table 5. First, a plasmid is directly isolated by screening the clones using a polynucleotide probe corresponding to the nucleotide sequence of SEQ ID NO:X.

[0793] Particularly, a specific polynucleotide with 30-40 nucleotides is synthesized using an Applied Biosystems DNA synthesizer according to the sequence reported. The oligonucleotide is labeled, for instance, with ^{32}P-γ-ATP using T4 polynucleotide kinase and purified according to routine methods. (E.g., Maniatis et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press, Cold Spring, NY (1982).) The plasmid mixture is transformed into a suitable host, as indicated above (such as XL-1 Blue (Stratagene)) using techniques known to those of skill in the art, such as those provided by the vector supplier or in related publications or patents cited above. The transformants are plated on 1.5% agar plates (containing the appropriate selection agent, e.g., ampicillin) to a density of about 150 transformants (colonies) per plate. These plates are screened using Nylon membranes according to routine methods for bacterial colony screening (e.g., Sambrook et al., Molecular Cloning: A Laboratory Manual, 2nd Edit., (1989), Cold Spring Harbor Laboratory Press, pages 1.93 to 1.104), or other techniques known to those of skill in the art.

[0794] Alternatively, two primers of 17-20 nucleotides derived from both ends of the nucleotide sequence of SEQ ID NO:X are synthesized and used to amplify the desired cDNA using the deposited cDNA plasmid as a template. The polymerase chain reaction is carried out under routine conditions, for instance, in 25 μl of reaction mixture with 0.5 ug of the above cDNA template. A convenient reaction mixture is 1.5-5 mM $MgCl_2$, 0.01% (w/v) gelatin, 20 μM each of dATP, dCTP, dGTP, dTTP, 25 pmol of each primer and 0.25 Unit of Taq polymerase. Thirty five cycles of PCR (denaturation at 94°C for 1 min; annealing at 55°C for 1 min; elongation at 72°C for 1 min) are performed with a Perkin-Elmer Cetus automated thermal cycler. The amplified product is analyzed by agarose gel electrophoresis and the DNA band with expected molecular weight is excised and purified. The PCR product is verified to be the selected sequence by subcloning and sequencing the DNA product.

[0795] Several methods are available for the identification of the 5' or 3' non-coding portions of a gene which may not be present in the deposited clone. These methods

include but are not limited to, filter probing, clone enrichment using specific probes, and protocols similar or identical to 5' and 3' "RACE" protocols which are well known in the art. For instance, a method similar to 5' RACE is available for generating the missing 5' end of a desired full-length transcript. (Fromont-Racine et al., Nucleic Acids Res. 21(7):1683-1684 (1993).)

[0796] Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a population of RNA presumably containing full-length gene RNA transcripts. A primer set containing a primer specific to the ligated RNA oligonucleotide and a primer specific to a known sequence of the gene of interest is used to PCR amplify the 5' portion of the desired full-length gene. This amplified product may then be sequenced and used to generate the full length gene.

[0797] This above method starts with total RNA isolated from the desired source, although poly-A+ RNA can be used. The RNA preparation can then be treated with phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase should then be inactivated and the RNA treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5' ends of messenger RNAs. This reaction leaves a 5' phosphate group at the 5' end of the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase.

[0798] This modified RNA preparation is used as a template for first strand cDNA synthesis using a gene specific oligonucleotide. The first strand synthesis reaction is used as a template for PCR amplification of the desired 5' end using a primer specific to the ligated RNA oligonucleotide and a primer specific to the known sequence of the gene of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the desired gene.

Example 2: Isolation of Genomic Clones Corresponding to a Polynucleotide

[0799] A human genomic P1 library (Genomic Systems, Inc.) is screened by PCR using primers selected for the sequence corresponding to SEQ ID NO:X, according to the method described in Example 1. (See also, Sambrook.)

Example 3: Tissue specific expression analysis

[0800] The Human Genome Sciences, Inc. (HGS) database is derived from sequencing tissue specific cDNA libraries. Libraries generated from a particular tissue are selected and the specific tissue expression pattern of EST groups or assembled contigs within these libraries is determined by comparison of the expression patterns of those groups or contigs within the entire database. ESTs which show tissue specific expression are selected.

[0801] The original clone from which the specific EST sequence was generated, is obtained from the catalogued library of clones and the insert amplified by PCR using methods known in the art. The PCR product is denatured then transferred in 96 well format to a nylon membrane (Schleicher and Scheull) generating an array filter of tissue specific clones. Housekeeping genes, maize genes, and known tissue specific genes are included on the filters. These targets can be used in signal normalization and to validate assay sensitivity. Additional targets are included to monitor probe length and specificity of hybridization.

[0802] Radioactively labeled hybridization probes are generated by first strand cDNA synthesis per the manufacturer's instructions (Life Technologies) from mRNA/RNA samples prepared from the specific tissue being analyzed. The hybridization probes are purified by gel exclusion chromatography, quantitated, and hybridized with the array filters in hybridization bottles at 65°C overnight. The filters are washed under stringent conditions and signals are captured using a Fuji phosphorimager.

[0803] Data is extracted using AIS software and following background subtraction, signal normalization is performed. This includes a normalization of filter-wide expression levels between different experimental runs. Genes that are differentially expressed in the tissue of interest are identified and the full length sequence of these clones is generated.

Example 4: Chromosomal Mapping of the Polynucleotides

[0804] An oligonucleotide primer set is designed according to the sequence at the 5' end of SEQ ID NO:X. This primer preferably spans about 100 nucleotides. This primer set is then used in a polymerase chain reaction under the following set of conditions : 30 seconds, 95°C; 1 minute, 56°C; 1 minute, 70°C. This cycle is repeated 32 times followed by one 5 minute cycle at 70°C. Human, mouse, and hamster DNA is used as template in addition to a somatic cell hybrid panel containing individual chromosomes or chromosome fragments (Bios, Inc). The reactions is analyzed on either 8% polyacrylamide gels or 3.5 % agarose gels. Chromosome mapping is determined by the presence of an approximately 100 bp PCR fragment in the particular somatic cell hybrid.

Example 5: Bacterial Expression of a Polypeptide

[0805] A polynucleotide encoding a polypeptide of the present invention is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' ends of the DNA sequence, as outlined in Example 1, to synthesize insertion fragments. The primers used to amplify the cDNA insert should preferably contain restriction sites, such as BamHI and XbaI, at the 5' end of the primers in order to clone the amplified product into the expression vector. For example, BamHI and XbaI correspond to the restriction enzyme sites on the bacterial expression vector pQE-9. (Qiagen, Inc., Chatsworth, CA). This plasmid vector encodes antibiotic resistance (Amp^r), a bacterial origin of replication (ori), an IPTG-regulatable promoter/operator (P/O), a ribosome binding site (RBS), a 6-histidine tag (6-His), and restriction enzyme cloning sites.

[0806] The pQE-9 vector is digested with BamHI and XbaI and the amplified fragment is ligated into the pQE-9 vector maintaining the reading frame initiated at the bacterial RBS. The ligation mixture is then used to transform the E. coli strain M15/rep4 (Qiagen, Inc.) which contains multiple copies of the plasmid pREP4, which expresses the lacI repressor and also confers kanamycin resistance (Kan^r). Transformants are identified by their ability to grow on LB plates and ampicillin/kanamycin resistant colonies are selected. Plasmid DNA is isolated and confirmed by restriction analysis.

[0807] Clones containing the desired constructs are grown overnight (O/N) in liquid culture in LB media supplemented with both Amp (100 ug/ml) and Kan (25 ug/ml). The O/N culture is used to inoculate a large culture at a ratio of 1:100 to 1:250. The cells are grown to an optical density 600 (O.D.^{600}) of between 0.4 and 0.6. IPTG (Isopropyl-B-D-thiogalacto pyranoside) is then added to a final concentration of 1 mM. IPTG induces by inactivating the lacI repressor, clearing the P/O leading to increased gene expression.

[0808] Cells are grown for an extra 3 to 4 hours. Cells are then harvested by centrifugation (20 mins at 6000Xg). The cell pellet is solubilized in the chaotropic agent 6 Molar Guanidine HCl by stirring for 3-4 hours at 4°C. The cell debris is removed by centrifugation, and the supernatant containing the polypeptide is loaded onto a nickel-nitrilo-tri-acetic acid ("Ni-NTA") affinity resin column (available from QIAGEN, Inc., *supra*). Proteins with a 6 x His tag bind to the Ni-NTA resin with high affinity and can be purified in a simple one-step procedure (for details see: The QIAexpressionist (1995) QIAGEN, Inc., *supra*).

[0809] Briefly, the supernatant is loaded onto the column in 6 M guanidine-HCl, pH 8, the column is first washed with 10 volumes of 6 M guanidine-HCl, pH 8, then washed with 10 volumes of 6 M guanidine-HCl pH 6, and finally the polypeptide is eluted with 6 M guanidine-HCl, pH 5.

[0810] The purified protein is then renatured by dialyzing it against phosphate-buffered saline (PBS) or 50 mM Na-acetate, pH 6 buffer plus 200 mM NaCl. Alternatively, the protein can be successfully refolded while immobilized on the Ni-NTA column. The recommended conditions are as follows: renature using a linear 6M-1M urea gradient in 500 mM NaCl, 20% glycerol, 20 mM Tris/HCl pH 7.4, containing protease inhibitors. The renaturation should be performed over a period of 1.5 hours or more. After renaturation the proteins are eluted by the addition of 250 mM immidazole. Immidazole is removed by a final dialyzing step against PBS or 50 mM sodium acetate pH 6 buffer plus 200 mM NaCl. The purified protein is stored at 4° C or frozen at -80° C.

[0811] In addition to the above expression vector, the present invention further includes an expression vector comprising phage operator and promoter elements operatively linked to a polynucleotide of the present invention, called pHE4a. (ATCC Accession Number 209645, deposited on February 25, 1998.) This vector contains: 1) a neomycinphosphotransferase gene as a selection marker, 2) an E. coli origin of replication,

3) a T5 phage promoter sequence, 4) two lac operator sequences, 5) a Shine-Delgarno sequence, and 6) the lactose operon repressor gene (lacIq). The origin of replication (oriC) is derived from pUC19 (LTI, Gaithersburg, MD). The promoter sequence and operator sequences are made synthetically.

[0812] DNA can be inserted into the pHEa by restricting the vector with NdeI and XbaI, BamHI, XhoI, or Asp718, running the restricted product on a gel, and isolating the larger fragment (the stuffer fragment should be about 310 base pairs). The DNA insert is generated according to the PCR protocol described in Example 1, using PCR primers having restriction sites for NdeI (5' primer) and XbaI, BamHI, XhoI, or Asp718 (3' primer). The PCR insert is gel purified and restricted with compatible enzymes. The insert and vector are ligated according to standard protocols.

[0813] The engineered vector could easily be substituted in the above protocol to express protein in a bacterial system.

Example 6: Purification of a Polypeptide from an Inclusion Body

[0814] The following alternative method can be used to purify a polypeptide expressed in *E coli* when it is present in the form of inclusion bodies. Unless otherwise specified, all of the following steps are conducted at 4-10°C.

[0815] Upon completion of the production phase of the *E. coli* fermentation, the cell culture is cooled to 4-10°C and the cells harvested by continuous centrifugation at 15,000 rpm (Heraeus Sepatech). On the basis of the expected yield of protein per unit weight of cell paste and the amount of purified protein required, an appropriate amount of cell paste, by weight, is suspended in a buffer solution containing 100 mM Tris, 50 mM EDTA, pH 7.4. The cells are dispersed to a homogeneous suspension using a high shear mixer.

[0816] The cells are then lysed by passing the solution through a microfluidizer (Microfuidics, Corp. or APV Gaulin, Inc.) twice at 4000-6000 psi. The homogenate is then mixed with NaCl solution to a final concentration of 0.5 M NaCl, followed by centrifugation at 7000 xg for 15 min. The resultant pellet is washed again using 0.5M NaCl, 100 mM Tris, 50 mM EDTA, pH 7.4.

[0817] The resulting washed inclusion bodies are solubilized with 1.5 M guanidine hydrochloride (GuHCl) for 2-4 hours. After 7000 xg centrifugation for 15 min., the pellet is discarded and the polypeptide containing supernatant is incubated at 4°C overnight to allow further GuHCl extraction.

[0818] Following high speed centrifugation (30,000 xg) to remove insoluble particles, the GuHCl solubilized protein is refolded by quickly mixing the GuHCl extract with 20 volumes of buffer containing 50 mM sodium, pH 4.5, 150 mM NaCl, 2 mM EDTA by vigorous stirring. The refolded diluted protein solution is kept at 4°C without mixing for 12 hours prior to further purification steps.

[0819] To clarify the refolded polypeptide solution, a previously prepared tangential filtration unit equipped with 0.16 μm membrane filter with appropriate surface area (e.g., Filtron), equilibrated with 40 mM sodium acetate, pH 6.0 is employed. The filtered sample is loaded onto a cation exchange resin (e.g., Poros HS-50, Perseptive Biosystems). The column is washed with 40 mM sodium acetate, pH 6.0 and eluted with 250 mM, 500 mM, 1000 mM, and 1500 mM NaCl in the same buffer, in a stepwise manner. The absorbance at 280 nm of the effluent is continuously monitored. Fractions are collected and further analyzed by SDS-PAGE.

[0820] Fractions containing the polypeptide are then pooled and mixed with 4 volumes of water. The diluted sample is then loaded onto a previously prepared set of tandem columns of strong anion (Poros HQ-50, Perseptive Biosystems) and weak anion (Poros CM-20, Perseptive Biosystems) exchange resins. The columns are equilibrated with 40 mM sodium acetate, pH 6.0. Both columns are washed with 40 mM sodium acetate, pH 6.0, 200 mM NaCl. The CM-20 column is then eluted using a 10 column volume linear gradient ranging from 0.2 M NaCl, 50 mM sodium acetate, pH 6.0 to 1.0 M NaCl, 50 mM sodium acetate, pH 6.5. Fractions are collected under constant A_{280} monitoring of the effluent. Fractions containing the polypeptide (determined, for instance, by 16% SDS-PAGE) are then pooled.

[0821] The resultant polypeptide should exhibit greater than 95% purity after the above refolding and purification steps. No major contaminant bands should be observed from Commassie blue stained 16% SDS-PAGE gel when 5 μg of purified protein is loaded. The purified protein can also be tested for endotoxin/LPS contamination, and typically the LPS content is less than 0.1 ng/ml according to LAL assays.

Example 7: Cloning and Expression of a Polypeptide in a Baculovirus Expression System

[0822] In this example, the plasmid shuttle vector pA2 is used to insert a polynucleotide into a baculovirus to express a polypeptide. This expression vector contains the strong polyhedrin promoter of the *Autographa californica* nuclear polyhedrosis virus (AcMNPV) followed by convenient restriction sites such as BamHI, Xba I and Asp718. The polyadenylation site of the simian virus 40 ("SV40") is used for efficient polyadenylation. For easy selection of recombinant virus, the plasmid contains the beta-galactosidase gene from *E. coli* under control of a weak Drosophila promoter in the same orientation, followed by the polyadenylation signal of the polyhedrin gene. The inserted genes are flanked on both sides by viral sequences for cell-mediated homologous recombination with wild-type viral DNA to generate a viable virus that express the cloned polynucleotide.

[0823] Many other baculovirus vectors can be used in place of the vector above, such as pAc373, pVL941, and pAcIM1, as one skilled in the art would readily appreciate, as long as the construct provides appropriately located signals for transcription, translation, secretion and the like, including a signal peptide and an in-frame AUG as required. Such vectors are described, for instance, in Luckow et al., Virology 170:31-39 (1989).

[0824] Specifically, the cDNA sequence contained in the deposited clone, including the AUG initiation codon, is amplified using the PCR protocol described in Example 1. If a naturally occurring signal sequence is used to produce the polypeptide of the present invention, the pA2 vector does not need a second signal peptide. Alternatively, the vector can be modified (pA2 GP) to include a baculovirus leader sequence, using the standard methods described in Summers et al., "A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures," Texas Agricultural Experimental Station Bulletin No. 1555 (1987).

[0825] The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("Geneclean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

[0826] The plasmid is digested with the corresponding restriction enzymes and optionally, can be dephosphorylated using calf intestinal phosphatase, using routine procedures known in the art. The DNA is then isolated from a 1% agarose gel using a commercially available kit ("Geneclean" BIO 101 Inc., La Jolla, Ca.).

[0827] The fragment and the dephosphorylated plasmid are ligated together with T4 DNA ligase. *E. coli* HB101 or other suitable *E. coli* hosts such as XL-1 Blue (Stratagene Cloning Systems, La Jolla, CA) cells are transformed with the ligation mixture and spread on culture plates. Bacteria containing the plasmid are identified by digesting DNA from individual colonies and analyzing the digestion product by gel electrophoresis. The sequence of the cloned fragment is confirmed by DNA sequencing.

[0828] Five μg of a plasmid containing the polynucleotide is co-transfected with 1.0 μg of a commercially available linearized baculovirus DNA ("BaculoGold™ baculovirus DNA", Pharmingen, San Diego, CA), using the lipofection method described by Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417 (1987). One μg of BaculoGold™ virus DNA and 5 μg of the plasmid are mixed in a sterile well of a microtiter plate containing 50 μl of serum-free Grace's medium (Life Technologies Inc., Gaithersburg, MD). Afterwards, 10 μl Lipofectin plus 90 μl Grace's medium are added, mixed and incubated for 15 minutes at room temperature. Then the transfection mixture is added drop-wise to Sf9 insect cells (ATCC CRL 1711) seeded in a 35 mm tissue culture plate with 1 ml Grace's medium without serum. The plate is then incubated for 5 hours at 27° C. The transfection solution is then removed from the plate and 1 ml of Grace's insect medium supplemented with 10% fetal calf serum is added. Cultivation is then continued at 27° C for four days.

[0829] After four days the supernatant is collected and a plaque assay is performed, as described by Summers and Smith, *supra*. An agarose gel with "Blue Gal" (Life Technologies Inc., Gaithersburg) is used to allow easy identification and isolation of gal-expressing clones, which produce blue-stained plaques. (A detailed description of a "plaque assay" of this type can also be found in the user's guide for insect cell culture and baculovirology distributed by Life Technologies Inc., Gaithersburg, page 9-10.) After appropriate incubation, blue stained plaques are picked with the tip of a micropipettor (e.g., Eppendorf). The agar containing the recombinant viruses is then resuspended in a microcentrifuge tube containing 200 μl of Grace's medium and the suspension containing

the recombinant baculovirus is used to infect Sf9 cells seeded in 35 mm dishes. Four days later the supernatants of these culture dishes are harvested and then they are stored at 4° C.

[0830] To verify the expression of the polypeptide, Sf9 cells are grown in Grace's medium supplemented with 10% heat-inactivated FBS. The cells are infected with the recombinant baculovirus containing the polynucleotide at a multiplicity of infection ("MOI") of about 2. If radiolabeled proteins are desired, 6 hours later the medium is removed and is replaced with SF900 II medium minus methionine and cysteine (available from Life Technologies Inc., Rockville, MD). After 42 hours, 5 μCi of ^{35}S-methionine and 5 μCi ^{35}S-cysteine (available from Amersham) are added. The cells are further incubated for 16 hours and then are harvested by centrifugation. The proteins in the supernatant as well as the intracellular proteins are analyzed by SDS-PAGE followed by autoradiography (if radiolabeled).

[0831] Microsequencing of the amino acid sequence of the amino terminus of purified protein may be used to determine the amino terminal sequence of the produced protein.

Example 8: Expression of a Polypeptide in Mammalian Cells

[0832] The polypeptide of the present invention can be expressed in a mammalian cell. A typical mammalian expression vector contains a promoter element, which mediates the initiation of transcription of mRNA, a protein coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription is achieved with the early and late promoters from SV40, the long terminal repeats (LTRs) from Retroviruses, e.g., RSV, HTLVI, HIVI and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (e.g., the human actin promoter).

[0833] Suitable expression vectors for use in practicing the present invention include, for example, vectors such as pSVL and pMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146), pBC12MI (ATCC 67109), pCMVSport 2.0, and pCMVSport 3.0. Mammalian host cells that could be used include, human Hela, 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and

CV1, quail QC1-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

[0834] Alternatively, the polypeptide can be expressed in stable cell lines containing the polynucleotide integrated into a chromosome. The co-transfection with a selectable marker such as DHFR, gpt, neomycin, hygromycin allows the identification and isolation of the transfected cells.

[0835] The transfected gene can also be amplified to express large amounts of the encoded protein. The DHFR (dihydrofolate reductase) marker is useful in developing cell lines that carry several hundred or even several thousand copies of the gene of interest. (See, e.g., Alt, F. W., et al., J. Biol. Chem. 253:1357-1370 (1978); Hamlin, J. L. and Ma, C., Biochem. et Biophys. Acta, 1097:107-143 (1990); Page, M. J. and Sydenham, M. A., Biotechnology 9:64-68 (1991).) Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy et al., Biochem J. 227:277-279 (1991); Bebbington et al., Bio/Technology 10:169-175 (1992). Using these markers, the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a chromosome. Chinese hamster ovary (CHO) and NSO cells are often used for the production of proteins.

[0836] Derivatives of the plasmid pSV2-dhfr (ATCC Accession No. 37146), the expression vectors pC4 (ATCC Accession No. 209646) and pC6 (ATCC Accession No.209647) contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen et al., Molecular and Cellular Biology, 438-447 (March, 1985)) plus a fragment of the CMV-enhancer (Boshart et al., Cell 41:521-530 (1985).) Multiple cloning sites, e.g., with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of the gene of interest. The vectors also contain the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene, and the mouse DHFR gene under control of the SV40 early promoter.

[0837] Specifically, the plasmid pC6, for example, is digested with appropriate restriction enzymes and then dephosphorylated using calf intestinal phosphates by procedures known in the art. The vector is then isolated from a 1% agarose gel.

A polynucleotide of the present invention is amplified according to the protocol outlined in Example 1. If a naturally occurring signal sequence is used to produce the polypeptide of the present invention, the vector does not need a second signal peptide. Alternatively, if a naturally occurring signal sequence is not used, the vector can be

modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

[0838] The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("Geneclean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

[0839] The amplified fragment is then digested with the same restriction enzyme and purified on a 1% agarose gel. The isolated fragment and the dephosphorylated vector are then ligated with T4 DNA ligase. *E. coli* HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC6 using, for instance, restriction enzyme analysis.

[0840] Chinese hamster ovary cells lacking an active DHFR gene is used for transfection. Five μg of the expression plasmid pC6 or pC4 is cotransfected with 0.5 μg of the plasmid pSVneo using lipofectin (Felgner et al., *supra*). The plasmid pSV2-neo contains a dominant selectable marker, the *neo* gene from Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1 mg/ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM supplemented with 10, 25, or 50 ng/ml of metothrexate plus 1 mg/ml G418. After about 10-14 days single clones are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well plates containing even higher concentrations of methotrexate (1 μM, 2 μM, 5 μM, 10 mM, 20 mM). The same procedure is repeated until clones are obtained which grow at a concentration of 100 - 200 μM. Expression of the desired gene product is analyzed, for instance, by SDS-PAGE and Western blot or by reversed phase HPLC analysis.

Example 9: Protein Fusions

[0841] The polypeptides of the present invention are preferably fused to other proteins. These fusion proteins can be used for a variety of applications. For example, fusion of the present polypeptides to His-tag, HA-tag, protein A, IgG domains, and maltose binding protein facilitates purification. (See Example 5; see also EP A 394,827;

Traunecker, et al., Nature 331:84-86 (1988).) Similarly, fusion to IgG-1, IgG-3, and albumin increases the halflife time in vivo. Nuclear localization signals fused to the polypeptides of the present invention can target the protein to a specific subcellular localization, while covalent heterodimer or homodimers can increase or decrease the activity of a fusion protein. Fusion proteins can also create chimeric molecules having more than one function. Finally, fusion proteins can increase solubility and/or stability of the fused protein compared to the non-fused protein. All of the types of fusion proteins described above can be made by modifying the following protocol, which outlines the fusion of a polypeptide to an IgG molecule, or the protocol described in Example 5.

[0842] Briefly, the human Fc portion of the IgG molecule can be PCR amplified, using primers that span the 5' and 3' ends of the sequence described below. These primers also should have convenient restriction enzyme sites that will facilitate cloning into an expression vector, preferably a mammalian expression vector.

[0843] For example, if pC4 (Accession No. 209646) is used, the human Fc portion can be ligated into the BamHI cloning site. Note that the 3' BamHI site should be destroyed. Next, the vector containing the human Fc portion is re-restricted with BamHI, linearizing the vector, and a polynucleotide of the present invention, isolated by the PCR protocol described in Example 1, is ligated into this BamHI site. Note that the polynucleotide is cloned without a stop codon, otherwise a fusion protein will not be produced.

[0844] If the naturally occurring signal sequence is used to produce the polypeptide of the present invention, pC4 does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

Human IgG Fc region:

GGGATCCGGAGCCCAAATCTTCTGACAAAACTCACACATGCCCACCGTGCCCA
GCACCTGAATTCGAGGGTGCACCGTCAGTCTTCCTCTTCCCCCCAAAACCCAA
GGACACCCTCATGATCTCCCGGACTCCTGAGGTCACATGCGTGGTGGTGGACG
TAAGCCACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGA
GGTGCATAATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTAC
CGTGTGGTCAGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGA

GTACAAGTGCAAGGTCTCCAACAAAGCCCTCCCAACCCCCATCGAGAAAACC
ATCTCCAAAGCCAAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCC
CATCCCGGGATGAGCTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAA
AGGCTTCTATCCAAGCGACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCG
GAGAACAACTACAAGACCACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTT
CCTCTACAGCAAGCTCACCGTGGACAAGAGCAGGTGGCAGCAGGGGAACGTC
TTCTCATGCTCCGTGATGCATGAGGCTCTGCACAACCACTACACGCAGAAGAG
CCTCTCCCTGTCTCCGGGTAAATGAGTGCGACGGCCGCGACTCTAGAGGAT
(SEQ ID NO:1881)

Example 10: Production of an Antibody from a Polypeptide

a) Hybridoma Technology

[0845] The antibodies of the present invention can be prepared by a variety of methods. (See, Current Protocols, Chapter 2.) As one example of such methods, cells expressing a polypeptide of the present invention are administered to an animal to induce the production of sera containing polyclonal antibodies. In a preferred method, a preparation of a polypeptide of the present invention is prepared and purified to render it substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.

[0846] Monoclonal antibodies specific for polypeptide of the present invention are prepared using hybridoma technology. (Kohler et al., Nature 256:495 (1975); Kohler et al., Eur. J. Immunol. 6:511 (1976); Kohler et al., Eur. J. Immunol. 6:292 (1976); Hammerling et al., in: Monoclonal Antibodies and T-Cell Hybridomas, Elsevier, N.Y., pp. 563-681 (1981)). In general, an animal (preferably a mouse) is immunized with polypeptide of the present invention or, more preferably, with a secreted polypeptide of the present invention-expressing cell. Such polypeptide-expressing cells are cultured in any suitable tissue culture medium, preferably in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at about 56°C), and supplemented with about 10 g/l of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100 μg/ml of streptomycin.

[0847] The splenocytes of such mice are extracted and fused with a suitable

myeloma cell line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP2O), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (Gastroenterology 80:225-232 (1981)). The hybridoma cells obtained through such a selection are then assayed to identify clones which secrete antibodies capable of binding the polypeptide of the present invention.

[0848] Alternatively, additional antibodies capable of binding to a polypeptide of the present invention can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the polypeptide of the present invention-specific antibody can be blocked by a polypeptide of the present invention. Such antibodies comprise anti-idiotypic antibodies to the polypeptide of the present invention-specific antibody and are used to immunize an animal to induce formation of further polypeptide of the present invention-specific antibodies.

[0849] For in vivo use of antibodies in humans, an antibody is "humanized". Such antibodies can be produced using genetic constructs derived from hybridoma cells producing the monoclonal antibodies described above. Methods for producing chimeric and humanized antibodies are known in the art and are discussed herein. (See, for review, Morrison, Science 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 (1985).)

b) Isolation Of Antibody Fragments Directed Against A Polypeptide of the Present Invention From A Library Of scFvs

Naturally occurring V-genes isolated from human PBLs are constructed into a library of antibody fragments which contain reactivities against a polypeptide of the present

invention to which the donor may or may not have been exposed (see e.g., U.S. Patent 5,885,793 incorporated herein by reference in its entirety).

Rescue of the Library. A library of scFvs is constructed from the RNA of human PBLs as described in PCT publication WO 92/01047. To rescue phage displaying antibody fragments, approximately 109 E. coli harboring the phagemid are used to inoculate 50 ml of 2xTY containing 1% glucose and 100 μg/ml of ampicillin (2xTY-AMP-GLU) and grown to an O.D. of 0.8 with shaking. Five ml of this culture is used to innoculate 50 ml of 2xTY-AMP-GLU, 2 x 108 TU of delta gene 3 helper (M13 delta gene III, see PCT publication WO 92/01047) are added and the culture incubated at 37°C for 45 minutes without shaking and then at 37°C for 45 minutes with shaking. The culture is centrifuged at 4000 r.p.m. for 10 min. and the pellet resuspended in 2 liters of 2xTY containing 100 μg/ml ampicillin and 50 ug/ml kanamycin and grown overnight. Phage are prepared as described in PCT publication WO 92/01047.

[0850] M13 delta gene III is prepared as follows: M13 delta gene III helper phage does not encode gene III protein, hence the phage(mid) displaying antibody fragments have a greater avidity of binding to antigen. Infectious M13 delta gene III particles are made by growing the helper phage in cells harboring a pUC19 derivative supplying the wild type gene III protein during phage morphogenesis. The culture is incubated for 1 hour at 37° C without shaking and then for a further hour at 37°C with shaking. Cells are spun down (IEC-Centra 8,400 r.p.m. for 10 min), resuspended in 300 ml 2xTY broth containing 100 μg ampicillin/ml and 25 μg kanamycin/ml (2xTY-AMP-KAN) and grown overnight, shaking at 37°C. Phage particles are purified and concentrated from the culture medium by two PEG-precipitations (Sambrook et al., 1990), resuspended in 2 ml PBS and passed through a 0.45 μm filter (Minisart NML; Sartorius) to give a final concentration of approximately 1013 transducing units/ml (ampicillin-resistant clones).

[0851] *Panning of the Library.* Immunotubes (Nunc) are coated overnight in PBS with 4 ml of either 100 μg/ml or 10 μg/ml of a polypeptide of the present invention. Tubes are blocked with 2% Marvel-PBS for 2 hours at 37°C and then washed 3 times in PBS. Approximately 1013 TU of phage is applied to the tube and incubated for 30 minutes at room temperature tumbling on an over and under turntable and then left to stand for another 1.5 hours. Tubes are washed 10 times with PBS 0.1% Tween-20 and 10 times with PBS. Phage are eluted by adding 1 ml of 100 mM triethylamine and rotating 15

minutes on an under and over turntable after which the solution is immediately neutralized with 0.5 ml of 1.0M Tris-HCl, pH 7.4. Phage are then used to infect 10 ml of mid-log E. coli TG1 by incubating eluted phage with bacteria for 30 minutes at 37°C. The E. coli are then plated on TYE plates containing 1% glucose and 100 μg/ml ampicillin. The resulting bacterial library is then rescued with delta gene 3 helper phage as described above to prepare phage for a subsequent round of selection. This process is then repeated for a total of 4 rounds of affinity purification with tube-washing increased to 20 times with PBS, 0.1% Tween-20 and 20 times with PBS for rounds 3 and 4.

[0852] *Characterization of Binders.* Eluted phage from the 3rd and 4th rounds of selection are used to infect E. coli HB 2151 and soluble scFv is produced (Marks, et al., 1991) from single colonies for assay. ELISAs are performed with microtitre plates coated with either 10 pg/ml of the polypeptide of the present invention in 50 mM bicarbonate pH 9.6. Clones positive in ELISA are further characterized by PCR fingerprinting (see, e.g., PCT publication WO 92/01047) and then by sequencing. These ELISA positive clones may also be further characterized by techniques known in the art, such as, for example, epitope mapping, binding affinity, receptor signal transduction, ability to block or competitively inhibit antibody/antigen binding, and competitive agonistic or antagonistic activity.

Example 11: Method of Determining Alterations in a Gene Corresponding to a Polynucleotide

[0853] RNA isolated from entire families or individual patients presenting with a phenotype of interest (such as a disease) is be isolated. cDNA is then generated from these RNA samples using protocols known in the art. (See, Sambrook.) The cDNA is then used as a template for PCR, employing primers surrounding regions of interest in SEQ ID NO:X; and/or the nucleotide sequence of the related cDNA in the cDNA clone contained in a deposited library. Suggested PCR conditions consist of 35 cycles at 95 degrees C for 30 seconds; 60-120 seconds at 52-58 degrees C; and 60-120 seconds at 70 degrees C, using buffer solutions described in Sidransky et al., Science 252:706 (1991).

[0854] PCR products are then sequenced using primers labeled at their 5' end with T4 polynucleotide kinase, employing SequiTherm Polymerase. (Epicentre Technologies).

The intron-exon borders of selected exons is also determined and genomic PCR products analyzed to confirm the results. PCR products harboring suspected mutations is then cloned and sequenced to validate the results of the direct sequencing.

[0855] PCR products is cloned into T-tailed vectors as described in Holton et al., Nucleic Acids Research, 19:1156 (1991) and sequenced with T7 polymerase (United States Biochemical). Affected individuals are identified by mutations not present in unaffected individuals.

[0856] Genomic rearrangements are also observed as a method of determining alterations in a gene corresponding to a polynucleotide. Genomic clones isolated according to Example 2 are nick-translated with digoxigenindeoxy-uridine 5'-triphosphate (Boehringer Manheim), and FISH performed as described in Johnson et al., Methods Cell Biol. 35:73-99 (1991). Hybridization with the labeled probe is carried out using a vast excess of human cot-1 DNA for specific hybridization to the corresponding genomic locus.

[0857] Chromosomes are counterstained with 4,6-diamino-2-phenylidole and propidium iodide, producing a combination of C- and R-bands. Aligned images for precise mapping are obtained using a triple-band filter set (Chroma Technology, Brattleboro, VT) in combination with a cooled charge-coupled device camera (Photometrics, Tucson, AZ) and variable excitation wavelength filters. (Johnson et al., Genet. Anal. Tech. Appl., 8:75 (1991).) Image collection, analysis and chromosomal fractional length measurements are performed using the ISee Graphical Program System. (Inovision Corporation, Durham, NC.) Chromosome alterations of the genomic region hybridized by the probe are identified as insertions, deletions, and translocations. These alterations are used as a diagnostic marker for an associated disease.

Example 12: Method of Detecting Abnormal Levels of a Polypeptide in a Biological Sample

[0858] A polypeptide of the present invention can be detected in a biological sample, and if an increased or decreased level of the polypeptide is detected, this polypeptide is a marker for a particular phenotype. Methods of detection are numerous, and thus, it is understood that one skilled in the art can modify the following assay to fit

their particular needs.

[0859] For example, antibody-sandwich ELISAs are used to detect polypeptides in a sample, preferably a biological sample. Wells of a microtiter plate are coated with specific antibodies, at a final concentration of 0.2 to 10 ug/ml. The antibodies are either monoclonal or polyclonal and are produced by the method described in Example 10. The wells are blocked so that non-specific binding of the polypeptide to the well is reduced.

[0860] The coated wells are then incubated for > 2 hours at RT with a sample containing the polypeptide. Preferably, serial dilutions of the sample should be used to validate results. The plates are then washed three times with deionized or distilled water to remove unbounded polypeptide.

[0861] Next, 50 ul of specific antibody-alkaline phosphatase conjugate, at a concentration of 25-400 ng, is added and incubated for 2 hours at room temperature. The plates are again washed three times with deionized or distilled water to remove unbounded conjugate.

[0862] Add 75 ul of 4-methylumbelliferyl phosphate (MUP) or p-nitrophenyl phosphate (NPP) substrate solution to each well and incubate 1 hour at room temperature. Measure the reaction by a microtiter plate reader. Prepare a standard curve, using serial dilutions of a control sample, and plot polypeptide concentration on the X-axis (log scale) and fluorescence or absorbance of the Y-axis (linear scale). Interpolate the concentration of the polypeptide in the sample using the standard curve.

Example 13: Formulation

[0863] The invention also provides methods of treatment and/or prevention of diseases or disorders (such as, for example, any one or more of the diseases or disorders disclosed herein) by administration to a subject of an effective amount of a Therapeutic. By therapeutic is meant a polynucleotides or polypeptides of the invention (including fragments and variants), agonists or antagonists thereof, and/or antibodies thereto, in combination with a pharmaceutically acceptable carrier type (e.g., a sterile carrier).

[0864] The Therapeutic will be formulated and dosed in a fashion consistent with good medical practice, taking into account the clinical condition of the individual patient (especially the side effects of treatment with the Therapeutic alone), the site of delivery,

the method of administration, the scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such considerations.

[0865] As a general proposition, the total pharmaceutically effective amount of the Therapeutic administered parenterally per dose will be in the range of about 1ug/kg/day to 10 mg/kg/day of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01 mg/kg/day, and most preferably for humans between about 0.01 and 1 mg/kg/day for the hormone. If given continuously, the Therapeutic is typically administered at a dose rate of about 1 ug/kg/hour to about 50 ug/kg/hour, either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following treatment for responses to occur appears to vary depending on the desired effect.

[0866] Therapeutics can be are administered orally, rectally, parenterally, intracistemally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), bucally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

[0867] Therapeutics of the invention are also suitably administered by sustained-release systems. Suitable examples of sustained-release Therapeutics are administered orally, rectally, parenterally, intracistemally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), bucally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

[0868] Therapeutics of the invention are also suitably administered by sustained-release systems. Suitable examples of sustained-release Therapeutics include suitable

polymeric materials (such as, for example, semi-permeable polymer matrices in the form of shaped articles, e.g., films, or mirocapsules), suitable hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, and sparingly soluble derivatives (such as, for example, a sparingly soluble salt).

[0869] Sustained-release matrices include polylactides (U.S. Pat. No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman et al., Biopolymers 22:547-556 (1983)), poly (2- hydroxyethyl methacrylate) (Langer et al., J. Biomed. Mater. Res. 15:167-277 (1981), and Langer, Chem. Tech. 12:98-105 (1982)), ethylene vinyl acetate (Langer et al., Id.) or poly-D- (-)-3-hydroxybutyric acid (EP 133,988).

[0870] Sustained-release Therapeutics also include liposomally entrapped Therapeutics of the invention (*see* generally, Langer, *Science* 249:1527-1533 (1990); Treat et al., in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 317 -327 and 353-365 (1989)). Liposomes containing the Therapeutic are prepared by methods known per se: DE 3,218,121; Epstein et al., Proc. Natl. Acad. Sci. (USA) 82:3688-3692 (1985); Hwang et al., Proc. Natl. Acad. Sci.(USA) 77:4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. percent cholesterol, the selected proportion being adjusted for the optimal Therapeutic.

[0871] In yet an additional embodiment, the Therapeutics of the invention are delivered by way of a pump (*see* Langer, *supra*; Sefton, CRC Crit. Ref. Biomed. Eng. 14:201 (1987); Buchwald et al., Surgery 88:507 (1980); Saudek et al., N. Engl. J. Med. 321:574 (1989)).

[0872] Other controlled release systems are discussed in the review by Langer (*Science* 249:1527-1533 (1990)).

[0873] For parenteral administration, in one embodiment, the Therapeutic is formulated generally by mixing it at the desired degree of purity, in a unit dosage injectable form (solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation. For example, the formulation

preferably does not include oxidizing agents and other compounds that are known to be deleterious to the Therapeutic.

[0874] Generally, the formulations are prepared by contacting the Therapeutic uniformly and intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier, more preferably a solution that is isotonic with the blood of the recipient. Examples of such carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-aqueous vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

[0875] The carrier suitably contains minor amounts of additives such as substances that enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, manose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic surfactants such as polysorbates, poloxamers, or PEG.

[0876] The Therapeutic is typically formulated in such vehicles at a concentration of about 0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will be understood that the use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of polypeptide salts.

[0877] Any pharmaceutical used for therapeutic administration can be sterile. Sterility is readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 micron membranes). Therapeutics generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

[0878] Therapeutics ordinarily will be stored in unit or multi-dose containers, for example, sealed ampoules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with

5 ml of sterile-filtered 1% (w/v) aqueous Therapeutic solution, and the resulting mixture is lyophilized. The infusion solution is prepared by reconstituting the lyophilized Therapeutic using bacteriostatic Water-for-Injection.

[0879] The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the Therapeutics of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, the Therapeutics may be employed in conjunction with other therapeutic compounds.

[0880] The Therapeutics of the invention may be administered alone or in combination with adjuvants. Adjuvants that may be administered with the Therapeutics of the invention include, but are not limited to, alum, alum plus deoxycholate (ImmunoAg), MTP-PE (Biocine Corp.), QS21 (Genentech, Inc.), BCG, and MPL. In a specific embodiment, Therapeutics of the invention are administered in combination with alum. In another specific embodiment, Therapeutics of the invention are administered in combination with QS-21. Further adjuvants that may be administered with the Therapeutics of the invention include, but are not limited to, Monophosphoryl lipid immunomodulator, AdjuVax 100a, QS-21, QS-18, CRL1005, Aluminum salts, MF-59, and Virosomal adjuvant technology. Vaccines that may be administered with the Therapeutics of the invention include, but are not limited to, vaccines directed toward protection against MMR (measles, mumps, rubella), polio, varicella, tetanus/diptheria, hepatitis A, hepatitis B, haemophilus influenzae B, whooping cough, pneumonia, influenza, Lyme's Disease, rotavirus, cholera, yellow fever, Japanese encephalitis, poliomyelitis, rabies, typhoid fever, and pertussis. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

[0881] The Therapeutics of the invention may be administered alone or in combination with other therapeutic agents. Therapeutic agents that may be administered in combination with the Therapeutics of the invention, include but not limited to, other members of the TNF family, chemotherapeutic agents, antibiotics, steroidal and non-steroidal anti-inflammatories, conventional immunotherapeutic agents, cytokines and/or growth factors. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

[0882] In one embodiment, the Therapeutics of the invention are administered in combination with members of the TNF family. TNF, TNF-related or TNF-like molecules that may be administered with the Therapeutics of the invention include, but are not limited to, soluble forms of TNF-alpha, lymphotoxin-alpha (LT-alpha, also known as TNF-beta), LT-beta (found in complex heterotrimer LT-alpha2-beta), OPGL, FasL, CD27L, CD30L, CD40L, 4-1BBL, DcR3, OX40L, TNF-gamma (International Publication No. WO 96/14328), AIM-I (International Publication No. WO 97/33899), endokine-alpha (International Publication No. WO 98/07880), TR6 (International Publication No. WO 98/30694), OPG, and neutrokine-alpha (International Publication No. WO 98/18921, OX40, and nerve growth factor (NGF), and soluble forms of Fas, CD30, CD27, CD40 and 4-IBB, TR2 (International Publication No. WO 96/34095), DR3 (International Publication No. WO 97/33904), DR4 (International Publication No. WO 98/32856), TR5 (International Publication No. WO 98/30693), TR6 (International Publication No. WO 98/30694), TR7 (International Publication No. WO 98/41629), TRANK, TR9 (International Publication No. WO 98/56892),TR10 (International Publication No. WO 98/54202), 312C2 (International Publication No. WO 98/06842), and TR12, and soluble forms CD154, CD70, and CD153.

[0883] In certain embodiments, Therapeutics of the invention are administered in combination with antiretroviral agents, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and/or protease inhibitors. Nucleoside reverse

transcriptase inhibitors that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, RETROVIR™ (zidovudine/AZT), VIDEX™ (didanosine/ddI), HIVID™ (zalcitabine/ddC), ZERIT™ (stavudine/d4T), EPIVIR™ (lamivudine/3TC), and COMBIVIR™ (zidovudine/lamivudine). Non-nucleoside reverse transcriptase inhibitors that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, VIRAMUNE™ (nevirapine), RESCRIPTOR™ (delavirdine), and SUSTIVA™ (efavirenz). Protease inhibitors that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, CRIXIVAN™ (indinavir), NORVIR™ (ritonavir), INVIRASE™ (saquinavir), and VIRACEPT™ (nelfinavir). In a specific embodiment, antiretroviral agents, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and/or protease inhibitors may be used in any combination with Therapeutics of the invention to treat AIDS and/or to prevent or treat HIV infection.

[0884] In other embodiments, Therapeutics of the invention may be administered in combination with anti-opportunistic infection agents. Anti-opportunistic agents that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, ATOVAQUONE™, ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, ETHAMBUTOL™, RIFABUTIN™, CLARITHROMYCIN™, AZITHROMYCIN™, GANCICLOVIR™, FOSCARNET™, CIDOFOVIR™, FLUCONAZOLE™, ITRACONAZOLE™, KETOCONAZOLE™, ACYCLOVIR™, FAMCICOLVIR™, PYRIMETHAMINE™, LEUCOVORIN™, NEUPOGEN™ (filgrastim/G-CSF), and LEUKINE™ (sargramostim/GM-CSF). In a specific embodiment, Therapeutics of the invention are used in any combination with TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, and/or ATOVAQUONE™ to prophylactically treat or prevent an opportunistic *Pneumocystis carinii* pneumonia infection. In another specific embodiment, Therapeutics of the invention are used in any combination with ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, and/or ETHAMBUTOL™ to prophylactically treat or prevent an opportunistic *Mycobacterium avium* complex infection. In another specific embodiment, Therapeutics of the invention are used in any combination with RIFABUTIN™,

CLARITHROMYCIN™, and/or AZITHROMYCIN™ to prophylactically treat or prevent an opportunistic *Mycobacterium tuberculosis* infection. In another specific embodiment, Therapeutics of the invention are used in any combination with GANCICLOVIR™, FOSCARNET™, and/or CIDOFOVIR™ to prophylactically treat or prevent an opportunistic cytomegalovirus infection. In another specific embodiment, Therapeutics of the invention are used in any combination with FLUCONAZOLE™, ITRACONAZOLE™, and/or KETOCONAZOLE™ to prophylactically treat or prevent an opportunistic fungal infection. In another specific embodiment, Therapeutics of the invention are used in any combination with ACYCLOVIR™ and/or FAMCICOLVIR™ to prophylactically treat or prevent an opportunistic herpes simplex virus type I and/or type II infection. In another specific embodiment, Therapeutics of the invention are used in any combination with PYRIMETHAMINE™ and/or LEUCOVORIN™ to prophylactically treat or prevent an opportunistic *Toxoplasma gondii* infection. In another specific embodiment, Therapeutics of the invention are used in any combination with LEUCOVORIN™ and/or NEUPOGEN™ to prophylactically treat or prevent an opportunistic bacterial infection.

[0885] In a further embodiment, the Therapeutics of the invention are administered in combination with an antiviral agent. Antiviral agents that may be administered with the Therapeutics of the invention include, but are not limited to, acyclovir, ribavirin, amantadine, and remantidine.

[0886] In a further embodiment, the Therapeutics of the invention are administered in combination with an antibiotic agent. Antibiotic agents that may be administered with the Therapeutics of the invention include, but are not limited to, amoxicillin, beta-lactamases, aminoglycosides, beta-lactam (glycopeptide), beta-lactamases, Clindamycin, chloramphenicol, cephalosporins, ciprofloxacin, ciprofloxacin, erythromycin, fluoroquinolones, macrolides, metronidazole, penicillins, quinolones, rifampin, streptomycin, sulfonamide, tetracyclines, trimethoprim, trimethoprim-sulfamthoxazole, and vancomycin.

[0887] Conventional nonspecific immunosuppressive agents, that may be administered in combination with the Therapeutics of the invention include, but are not limited to, steroids, cyclosporine, cyclosporine analogs, cyclophosphamide

methylprednisone, prednisone, azathioprine, FK-506, 15-deoxyspergualin, and other immunosuppressive agents that act by suppressing the function of responding T cells.

[0888] In specific embodiments, Therapeutics of the invention are administered in combination with immunosuppressants. Immunosuppressants preparations that may be administered with the Therapeutics of the invention include, but are not limited to, ORTHOCLONE™ (OKT3), SANDIMMUNE™/NEORAL™/SANGDYA™ (cyclosporin), PROGRAF™ (tacrolimus), CELLCEPT™ (mycophenolate), Azathioprine, glucorticosteroids, and RAPAMUNE™ (sirolimus). In a specific embodiment, immunosuppressants may be used to prevent rejection of organ or bone marrow transplantation.

[0889] In an additional embodiment, Therapeutics of the invention are administered alone or in combination with one or more intravenous immune globulin preparations. Intravenous immune globulin preparations that may be administered with the Therapeutics of the invention include, but not limited to, GAMMAR™, IVEEGAM™, SANDOGLOBULIN™, GAMMAGARD S/D™, and GAMIMUNE™. In a specific embodiment, Therapeutics of the invention are administered in combination with intravenous immune globulin preparations in transplantation therapy (e.g., bone marrow transplant).

[0890] In an additional embodiment, the Therapeutics of the invention are administered alone or in combination with an anti-inflammatory agent. Anti-inflammatory agents that may be administered with the Therapeutics of the invention include, but are not limited to, glucocorticoids and the nonsteroidal anti-inflammatories, aminoarylcarboxylic acid derivatives, arylacetic acid derivatives, arylbutyric acid derivatives, arylcarboxylic acids, arylpropionic acid derivatives, pyrazoles, pyrazolones, salicylic acid derivatives, thiazinecarboxamides, e-acetamidocaproic acid, S-adenosylmethionine, 3-amino-4-hydroxybutyric acid, amixetrine, bendazac, benzydamine, bucolome, difenpiramide, ditazol, emorfazone, guaiazulene, nabumetone, nimesulide, orgotein, oxaceprol, paranyline, perisoxal, pifoxime, proquazone, proxazole, and tenidap.

[0891] In another embodiment, compostions of the invention are administered in combination with a chemotherapeutic agent. Chemotherapeutic agents that may be administered with the Therapeutics of the invention include, but are not limited to,

antibiotic derivatives (e.g., doxorubicin, bleomycin, daunorubicin, and dactinomycin); antiestrogens (e.g., tamoxifen); antimetabolites (e.g., fluorouracil, 5-FU, methotrexate, floxuridine, interferon alpha-2b, glutamic acid, plicamycin, mercaptopurine, and 6-thioguanine); cytotoxic agents (e.g., carmustine, BCNU, lomustine, CCNU, cytosine arabinoside, cyclophosphamide, estramustine, hydroxyurea, procarbazine, mitomycin, busulfan, cis-platin, and vincristine sulfate); hormones (e.g., medroxyprogesterone, estramustine phosphate sodium, ethinyl estradiol, estradiol, megestrol acetate, methyltestosterone, diethylstilbestrol diphosphate, chlorotrianisene, and testolactone); nitrogen mustard derivatives (e.g., mephalen, chorambucil, mechlorethamine (nitrogen mustard) and thiotepa); steroids and combinations (e.g., bethamethasone sodium phosphate); and others (e.g., dicarbazine, asparaginase, mitotane, vincristine sulfate, vinblastine sulfate, and etoposide).

[0892] In a specific embodiment, Therapeutics of the invention are administered in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or any combination of the components of CHOP. In another embodiment, Therapeutics of the invention are administered in combination with Rituximab. In a further embodiment, Therapeutics of the invention are administered with Rituxmab and CHOP, or Rituxmab and any combination of the components of CHOP.

[0893] In an additional embodiment, the Therapeutics of the invention are administered in combination with cytokines. Cytokines that may be administered with the Therapeutics of the invention include, but are not limited to, IL2, IL3, IL4, IL5, IL6, IL7, IL10, IL12, IL13, IL15, anti-CD40, CD40L, IFN-gamma and TNF-alpha. In another embodiment, Therapeutics of the invention may be administered with any interleukin, including, but not limited to, IL-1alpha, IL-1beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, IL-19, IL-20, and IL-21.

[0894] In an additional embodiment, the Therapeutics of the invention are administered in combination with angiogenic proteins. Angiogenic proteins that may be administered with the Therapeutics of the invention include, but are not limited to, Glioma Derived Growth Factor (GDGF), as disclosed in European Patent Number EP-399816; Platelet Derived Growth Factor-A (PDGF-A), as disclosed in European Patent Number EP-682110; Platelet Derived Growth Factor-B (PDGF-B), as disclosed in European Patent

Number EP-282317; Placental Growth Factor (PlGF), as disclosed in International Publication Number WO 92/06194; Placental Growth Factor-2 (PlGF-2), as disclosed in Hauser et al., Gorwth Factors, 4:259-268 (1993); Vascular Endothelial Growth Factor (VEGF), as disclosed in International Publication Number WO 90/13649; Vascular Endothelial Growth Factor-A (VEGF-A), as disclosed in European Patent Number EP-506477; Vascular Endothelial Growth Factor-2 (VEGF-2), as disclosed in International Publication Number WO 96/39515; Vascular Endothelial Growth Factor B (VEGF-3); Vascular Endothelial Growth Factor B-186 (VEGF-B186), as disclosed in International Publication Number WO 96/26736; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/02543; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/07832; and Vascular Endothelial Growth Factor-E (VEGF-E), as disclosed in German Patent Number DE19639601. The above mentioned references are incorporated herein by reference herein.

[0895] In an additional embodiment, the Therapeutics of the invention are administered in combination with hematopoietic growth factors. Hematopoietic growth factors that may be administered with the Therapeutics of the invention include, but are not limited to, LEUKINE™ (SARGRAMOSTIM™) and NEUPOGEN™ (FILGRASTIM™).

[0896] In an additional embodiment, the Therapeutics of the invention are administered in combination with Fibroblast Growth Factors. Fibroblast Growth Factors that may be administered with the Therapeutics of the invention include, but are not limited to, FGF-1, FGF-2, FGF-3, FGF-4, FGF-5, FGF-6, FGF-7, FGF-8, FGF-9, FGF-10, FGF-11, FGF-12, FGF-13, FGF-14, and FGF-15.

[0897] In additional embodiments, the Therapeutics of the invention are administered in combination with other therapeutic or prophylactic regimens, such as, for example, radiation therapy.

Example 14: Method of Treating Decreased Levels of the Polypeptide

[0898] The present invention relates to a method for treating an individual in need of an increased level of a polypeptide of the invention in the body comprising

administering to such an individual a composition comprising a therapeutically effective amount of an agonist of the invention (including polypeptides of the invention). Moreover, it will be appreciated that conditions caused by a decrease in the standard or normal expression level of a polypeptide of the present invention in an individual can be treated by administering the agonist or antagonist of the present invention. Thus, the invention also provides a method of treatment of an individual in need of an increased level of the polypeptide comprising administering to such an individual a Therapeutic comprising an amount of the agonist or antagonist to increase the activity level of the polypeptide in such an individual.

[0899] For example, a patient with decreased levels of a polypeptide receives a daily dose 0.1-100 ug/kg of the agonist or antagonist for six consecutive days. The exact details of the dosing scheme, based on administration and formulation, are provided in Example 13.

Example 15: Method of Treating Increased Levels of the Polypeptide

[0900] The present invention also relates to a method of treating an individual in need of a decreased level of a polypeptide of the invention in the body comprising administering to such an individual a composition comprising a therapeutically effective amount of an antagonist of the invention (including polypeptides and antibodies of the invention).

[0901] In one example, antisense technology is used to inhibit production of a polypeptide of the present invention. This technology is one example of a method of decreasing levels of a polypeptide, due to a variety of etiologies, such as cancer.

[0902] For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously antisense polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the antisense polynucleotide is provided in Example 13.

Example 16: Method of Treatment Using Gene Therapy-Ex Vivo

[0903] One method of gene therapy transplants fibroblasts, which are capable of expressing a polypeptide, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and separated into small pieces. Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately ten pieces are placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e.g., Ham's F12 media, with 10% FBS, penicillin and streptomycin) is added. The flasks are then incubated at 37 degree C for approximately one week.

[0904] At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer is trypsinized and scaled into larger flasks.

[0905] pMV-7 (Kirschmeier, P.T. et al., DNA, 7:219-25 (1988)), flanked by the long terminal repeats of the Moloney murine sarcoma virus, is digested with EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on agarose gel and purified, using glass beads.

[0906] The cDNA encoding a polypeptide of the present invention can be amplified using PCR primers which correspond to the 5' and 3' end sequences respectively as set forth in Example 1 using primers and having appropriate restriction sites and initiation/stop codons, if necessary. Preferably, the 5' primer contains an EcoRI site and the 3' primer includes a HindIII site. Equal quantities of the Moloney murine sarcoma virus linear backbone and the amplified EcoRI and HindIII fragment are added together, in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The ligation mixture is then used to transform bacteria HB101, which are then plated onto agar containing kanamycin for the purpose of confirming that the vector has the gene of interest properly inserted.

[0907] The amphotropic pA317 or GP+am12 packaging cells are grown in tissue culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with 10% calf serum (CS), penicillin and streptomycin. The MSV vector containing the gene is then added to the media and the packaging cells transduced with the vector. The packaging cells now produce infectious viral particles containing the gene (the packaging cells are

now referred to as producer cells).

[0908] Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media, containing the infectious viral particles, is filtered through a millipore filter to remove detached producer cells and this media is then used to infect fibroblast cells. Media is removed from a sub-confluent plate of fibroblasts and quickly replaced with the media from the producer cells. This media is removed and replaced with fresh media. If the titer of virus is high, then virtually all fibroblasts will be infected and no selection is required. If the titer is very low, then it is necessary to use a retroviral vector that has a selectable marker, such as neo or his. Once the fibroblasts have been efficiently infected, the fibroblasts are analyzed to determine whether protein is produced.

[0909] The engineered fibroblasts are then transplanted onto the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads.

Example 17: Gene Therapy Using Endogenous Genes Corresponding To Polynucleotides of the Invention

[0910] Another method of gene therapy according to the present invention involves operably associating the endogenous polynucleotide sequence of the invention with a promoter via homologous recombination as described, for example, in U.S. Patent NO: 5,641,670, issued June 24, 1997; International Publication NO: WO 96/29411, published September 26, 1996; International Publication NO: WO 94/12650, published August 4, 1994; Koller et al., *Proc. Natl. Acad. Sci. USA,* 86:8932-8935 (1989); and Zijlstra et al., *Nature,* 342:435-438 (1989). This method involves the activation of a gene which is present in the target cells, but which is not expressed in the cells, or is expressed at a lower level than desired.

[0911] Polynucleotide constructs are made which contain a promoter and targeting sequences, which are homologous to the 5' non-coding sequence of endogenous polynucleotide sequence, flanking the promoter. The targeting sequence will be sufficiently near the 5' end of the polynucleotide sequence so the promoter will be operably linked to the endogenous sequence upon homologous recombination. The promoter and the targeting sequences can be amplified using PCR. Preferably, the

amplified promoter contains distinct restriction enzyme sites on the 5' and 3' ends. Preferably, the 3' end of the first targeting sequence contains the same restriction enzyme site as the 5' end of the amplified promoter and the 5' end of the second targeting sequence contains the same restriction site as the 3' end of the amplified promoter.

[0912] The amplified promoter and the amplified targeting sequences are digested with the appropriate restriction enzymes and subsequently treated with calf intestinal phosphatase. The digested promoter and digested targeting sequences are added together in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The construct is size fractionated on an agarose gel then purified by phenol extraction and ethanol precipitation.

[0913] In this Example, the polynucleotide constructs are administered as naked polynucleotides via electroporation. However, the polynucleotide constructs may also be administered with transfection-facilitating agents, such as liposomes, viral sequences, viral particles, precipitating agents, etc. Such methods of delivery are known in the art.

[0914] Once the cells are transfected, homologous recombination will take place which results in the promoter being operably linked to the endogenous polynucleotide sequence. This results in the expression of polynucleotide corresponding to the polynucleotide in the cell. Expression may be detected by immunological staining, or any other method known in the art.

[0915] Fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in DMEM + 10% fetal calf serum. Exponentially growing or early stationary phase fibroblasts are trypsinized and rinsed from the plastic surface with nutrient medium. An aliquot of the cell suspension is removed for counting, and the remaining cells are subjected to centrifugation. The supernatant is aspirated and the pellet is resuspended in 5 ml of electroporation buffer (20 mM HEPES pH 7.3, 137 mM NaCl, 5 mM KCl, 0.7 mM Na_2HPO_4, 6 mM dextrose). The cells are recentrifuged, the supernatant aspirated, and the cells resuspended in electroporation buffer containing 1 mg/ml acetylated bovine serum albumin. The final cell suspension contains approximately $3X10^6$ cells/ml. Electroporation should be performed immediately following resuspension.

[0916] Plasmid DNA is prepared according to standard techniques. For example, to construct a plasmid for targeting to the locus corresponding to the polynucleotide of the invention, plasmid pUC18 (MBI Fermentas, Amherst, NY) is digested with HindIII. The

CMV promoter is amplified by PCR with an XbaI site on the 5' end and a BamHI site on the 3'end. Two non-coding sequences are amplified via PCR: one non-coding sequence (fragment 1) is amplified with a HindIII site at the 5' end and an Xba site at the 3'end; the other non-coding sequence (fragment 2) is amplified with a BamHI site at the 5'end and a HindIII site at the 3'end. The CMV promoter and the fragments (1 and 2) are digested with the appropriate enzymes (CMV promoter - XbaI and BamHI; fragment 1 - XbaI; fragment 2 - BamHI) and ligated together. The resulting ligation product is digested with HindIII, and ligated with the HindIII-digested pUC18 plasmid.

[0917] Plasmid DNA is added to a sterile cuvette with a 0.4 cm electrode gap (Bio-Rad). The final DNA concentration is generally at least 120 μg/ml. 0.5 ml of the cell suspension (containing approximately 1.5.X10^6 cells) is then added to the cuvette, and the cell suspension and DNA solutions are gently mixed. Electroporation is performed with a Gene-Pulser apparatus (Bio-Rad). Capacitance and voltage are set at 960 μF and 250-300 V, respectively. As voltage increases, cell survival decreases, but the percentage of surviving cells that stably incorporate the introduced DNA into their genome increases dramatically. Given these parameters, a pulse time of approximately 14-20 mSec should be observed.

[0918] Electroporated cells are maintained at room temperature for approximately 5 min, and the contents of the cuvette are then gently removed with a sterile transfer pipette. The cells are added directly to 10 ml of prewarmed nutrient media (DMEM with 15% calf serum) in a 10 cm dish and incubated at 37 degree C. The following day, the media is aspirated and replaced with 10 ml of fresh media and incubated for a further 16-24 hours.

[0919] The engineered fibroblasts are then injected into the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads. The fibroblasts now produce the protein product. The fibroblasts can then be introduced into a patient as described above.

Example 18: Method of Treatment Using Gene Therapy - In Vivo

[0920] Another aspect of the present invention is using *in vivo* gene therapy methods to treat disorders, diseases and conditions. The gene therapy method relates to

the introduction of naked nucleic acid (DNA, RNA, and antisense DNA or RNA) sequences into an animal to increase or decrease the expression of the polypeptide. The polynucleotide of the present invention may be operatively linked to a promoter or any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques and methods are known in the art, see, for example, WO90/11092, WO98/11779; U.S. Patent NO. 5693622, 5705151, 5580859; Tabata et al., Cardiovasc. Res. 35(3):470-479 (1997); Chao et al., Pharmacol. Res. 35(6):517-522 (1997); Wolff, Neuromuscul. Disord. 7(5):314-318 (1997); Schwartz et al., Gene Ther. 3(5):405-411 (1996); Tsurumi et al., Circulation 94(12):3281-3290 (1996) (incorporated herein by reference).

[0921] The polynucleotide constructs may be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, intestine and the like). The polynucleotide constructs can be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

[0922] The term "naked" polynucleotide, DNA or RNA, refers to sequences that are free from any delivery vehicle that acts to assist, promote, or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotides of the present invention may also be delivered in liposome formulations (such as those taught in Felgner P.L. et al. (1995) Ann. NY Acad. Sci. 772:126-139 and Abdallah B. et al. (1995) Biol. Cell 85(1):1-7) which can be prepared by methods well known to those skilled in the art.

[0923] The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Any strong promoter known to those skilled in the art can be used for driving the expression of DNA. Unlike other gene therapies techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

[0924] The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder,

stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

[0925] For the naked polynucleotide injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 g/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration. The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked polynucleotide constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

[0926] The dose response effects of injected polynucleotide in muscle *in vivo* is determined as follows. Suitable template DNA for production of mRNA coding for polypeptide of the present invention is prepared in accordance with a standard recombinant DNA methodology. The template DNA, which may be either circular or linear, is either used as naked DNA or complexed with liposomes. The quadriceps muscles of mice are then injected with various amounts of the template DNA.

[0927] Five to six week old female and male Balb/C mice are anesthetized by intraperitoneal injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on the anterior thigh, and the quadriceps muscle is directly visualized. The template DNA is injected in 0.1 ml of carrier in a 1 cc syringe through a 27 gauge needle over one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about 0.2 cm deep. A suture is placed over the injection site for future localization, and the skin is closed with stainless steel clips.

[0928] After an appropriate incubation time (e.g., 7 days) muscle extracts are prepared by excising the entire quadriceps. Every fifth 15 um cross-section of the individual quadriceps muscles is histochemically stained for protein expression. A time course for protein expression may be done in a similar fashion except that quadriceps from different mice are harvested at different times. Persistence of DNA in muscle following injection may be determined by Southern blot analysis after preparing total cellular DNA and HIRT supernatants from injected and control mice. The results of the above experimentation in mice can be use to extrapolate proper dosages and other treatment parameters in humans and other animals using naked DNA.

Example 19: Transgenic Animals

[0929] The polypeptides of the invention can also be expressed in transgenic animals. Animals of any species, including, but not limited to, mice, rats, rabbits, hamsters, guinea pigs, pigs, micro-pigs, goats, sheep, cows and non-human primates, *e.g.*, baboons, monkeys, and chimpanzees may be used to generate transgenic animals. In a specific embodiment, techniques described herein or otherwise known in the art, are used to express polypeptides of the invention in humans, as part of a gene therapy protocol.

[0930] Any technique known in the art may be used to introduce the transgene (i.e., polynucleotides of the invention) into animals to produce the founder lines of transgenic animals. Such techniques include, but are not limited to, pronuclear microinjection (Paterson et al., Appl. Microbiol. Biotechnol. 40:691-698 (1994); Carver et al., Biotechnology (NY) 11:1263-1270 (1993); Wright et al., Biotechnology (NY) 9:830-834 (1991); and Hoppe et al., U.S. Pat. No. 4,873,191 (1989)); retrovirus mediated gene transfer into germ lines (Van der Putten et al., Proc. Natl. Acad. Sci., USA 82:6148-6152

(1985)), blastocysts or embryos; gene targeting in embryonic stem cells (Thompson et al., Cell 56:313-321 (1989)); electroporation of cells or embryos (Lo, 1983, Mol Cell. Biol. 3:1803-1814 (1983)); introduction of the polynucleotides of the invention using a gene gun (see, e.g., Ulmer et al., Science 259:1745 (1993); introducing nucleic acid constructs into embryonic pleuripotent stem cells and transferring the stem cells back into the blastocyst; and sperm-mediated gene transfer (Lavitrano et al., Cell 57:717-723 (1989); etc. For a review of such techniques, see Gordon, "Transgenic Animals," Intl. Rev. Cytol. 115:171-229 (1989), which is incorporated by reference herein in its entirety.

[0931] Any technique known in the art may be used to produce transgenic clones containing polynucleotides of the invention, for example, nuclear transfer into enucleated oocytes of nuclei from cultured embryonic, fetal, or adult cells induced to quiescence (Campell et al., Nature 380:64-66 (1996); Wilmut et al., Nature 385:810-813 (1997)).

[0932] The present invention provides for transgenic animals that carry the transgene in all their cells, as well as animals which carry the transgene in some, but not all their cells, *i.e.,* mosaic animals or chimeric. The transgene may be integrated as a single transgene or as multiple copies such as in concatamers, *e.g.,* head-to-head tandems or head-to-tail tandems. The transgene may also be selectively introduced into and activated in a particular cell type by following, for example, the teaching of Lasko et al. (Lasko et al., Proc. Natl. Acad. Sci. USA 89:6232-6236 (1992)). The regulatory sequences required for such a cell-type specific activation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art. When it is desired that the polynucleotide transgene be integrated into the chromosomal site of the endogenous gene, gene targeting is preferred. Briefly, when such a technique is to be utilized, vectors containing some nucleotide sequences homologous to the endogenous gene are designed for the purpose of integrating, via homologous recombination with chromosomal sequences, into and disrupting the function of the nucleotide sequence of the endogenous gene. The transgene may also be selectively introduced into a particular cell type, thus inactivating the endogenous gene in only that cell type, by following, for example, the teaching of Gu et al. (Gu et al., Science 265:103-106 (1994)). The regulatory sequences required for such a cell-type specific inactivation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art.

[0933] Once transgenic animals have been generated, the expression of the

recombinant gene may be assayed utilizing standard techniques. Initial screening may be accomplished by Southern blot analysis or PCR techniques to analyze animal tissues to verify that integration of the transgene has taken place. The level of mRNA expression of the transgene in the tissues of the transgenic animals may also be assessed using techniques which include, but are not limited to, Northern blot analysis of tissue samples obtained from the animal, *in situ* hybridization analysis, and reverse transcriptase-PCR (rt-PCR). Samples of transgenic gene-expressing tissue may also be evaluated immunocytochemically or immunohistochemically using antibodies specific for the transgene product.

[0934] Once the founder animals are produced, they may be bred, inbred, outbred, or crossbred to produce colonies of the particular animal. Examples of such breeding strategies include, but are not limited to: outbreeding of founder animals with more than one integration site in order to establish separate lines; inbreeding of separate lines in order to produce compound transgenics that express the transgene at higher levels because of the effects of additive expression of each transgene; crossing of heterozygous transgenic animals to produce animals homozygous for a given integration site in order to both augment expression and eliminate the need for screening of animals by DNA analysis; crossing of separate homozygous lines to produce compound heterozygous or homozygous lines; and breeding to place the transgene on a distinct background that is appropriate for an experimental model of interest.

[0935] Transgenic animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

Example 20: Knock-Out Animals

[0936] Endogenous gene expression can also be reduced by inactivating or "knocking out" the gene and/or its promoter using targeted homologous recombination. (*E.g.*, see Smithies et al., Nature 317:230-234 (1985); Thomas & Capecchi, Cell 51:503-512 (1987); Thompson et al., Cell 5:313-321 (1989); each of which is incorporated by

reference herein in its entirety). For example, a mutant, non-functional polynucleotide of the invention (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous polynucleotide sequence (either the coding regions or regulatory regions of the gene) can be used, with or without a selectable marker and/or a negative selectable marker, to transfect cells that express polypeptides of the invention *in vivo*. In another embodiment, techniques known in the art are used to generate knockouts in cells that contain, but do not express the gene of interest. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the targeted gene. Such approaches are particularly suited in research and agricultural fields where modifications to embryonic stem cells can be used to generate animal offspring with an inactive targeted gene (*e.g.*, see Thomas & Capecchi 1987 and Thompson 1989, *supra*). However this approach can be routinely adapted for use in humans provided the recombinant DNA constructs are directly administered or targeted to the required site *in vivo* using appropriate viral vectors that will be apparent to those of skill in the art.

[0937] In further embodiments of the invention, cells that are genetically engineered to express the polypeptides of the invention, or alternatively, that are genetically engineered not to express the polypeptides of the invention (e.g., knockouts) are administered to a patient *in vivo*. Such cells may be obtained from the patient (i.e., animal, including human) or an MHC compatible donor and can include, but are not limited to fibroblasts, bone marrow cells, blood cells (e.g., lymphocytes), adipocytes, muscle cells, endothelial cells etc. The cells are genetically engineered *in vitro* using recombinant DNA techniques to introduce the coding sequence of polypeptides of the invention into the cells, or alternatively, to disrupt the coding sequence and/or endogenous regulatory sequence associated with the polypeptides of the invention, e.g., by transduction (using viral vectors, and preferably vectors that integrate the transgene into the cell genome) or transfection procedures, including, but not limited to, the use of plasmids, cosmids, YACs, naked DNA, electroporation, liposomes, etc. The coding sequence of the polypeptides of the invention can be placed under the control of a strong constitutive or inducible promoter or promoter/enhancer to achieve expression, and preferably secretion, of the polypeptides of the invention. The engineered cells which express and preferably secrete the polypeptides of the invention can be introduced into the patient systemically, e.g., in the circulation, or intraperitoneally.

[0938] Alternatively, the cells can be incorporated into a matrix and implanted in the body, e.g., genetically engineered fibroblasts can be implanted as part of a skin graft; genetically engineered endothelial cells can be implanted as part of a lymphatic or vascular graft. (See, for example, Anderson et al. U.S. Patent No. 5,399,349; and Mulligan & Wilson, U.S. Patent No. 5,460,959 each of which is incorporated by reference herein in its entirety).

[0939] When the cells to be administered are non-autologous or non-MHC compatible cells, they can be administered using well known techniques which prevent the development of a host immune response against the introduced cells. For example, the cells may be introduced in an encapsulated form which, while allowing for an exchange of components with the immediate extracellular environment, does not allow the introduced cells to be recognized by the host immune system.

[0940] Transgenic and "knock-out" animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

Example 21: Assays Detecting Stimulation or Inhibition of B cell Proliferation and Differentiation

[0941] Generation of functional humoral immune responses requires both soluble and cognate signaling between B-lineage cells and their microenvironment. Signals may impart a positive stimulus that allows a B-lineage cell to continue its programmed development, or a negative stimulus that instructs the cell to arrest its current developmental pathway. To date, numerous stimulatory and inhibitory signals have been found to influence B cell responsiveness including IL-2, IL-4, IL-5, IL-6, IL-7, IL10, IL-13, IL-14 and IL-15. Interestingly, these signals are by themselves weak effectors but can, in combination with various co-stimulatory proteins, induce activation, proliferation, differentiation, homing, tolerance and death among B cell populations.

[0942] One of the best studied classes of B-cell co-stimulatory proteins is the TNF-superfamily. Within this family CD40, CD27, and CD30 along with their respective

ligands CD154, CD70, and CD153 have been found to regulate a variety of immune responses. Assays which allow for the detection and/or observation of the proliferation and differentiation of these B-cell populations and their precursors are valuable tools in determining the effects various proteins may have on these B-cell populations in terms of proliferation and differentiation. Listed below are two assays designed to allow for the detection of the differentiation, proliferation, or inhibition of B-cell populations and their precursors.

[0943] **In Vitro Assay**- Agonists or antagonists of the invention can be assessed for its ability to induce activation, proliferation, differentiation or inhibition and/or death in B-cell populations and their precursors. The activity of the agonists or antagonists of the invention on purified human tonsillar B cells, measured qualitatively over the dose range from 0.1 to 10,000 ng/mL, is assessed in a standard B-lymphocyte co-stimulation assay in which purified tonsillar B cells are cultured in the presence of either formalin-fixed Staphylococcus aureus Cowan I (SAC) or immobilized anti-human IgM antibody as the priming agent. Second signals such as IL-2 and IL-15 synergize with SAC and IgM crosslinking to elicit B cell proliferation as measured by tritiated-thymidine incorporation. Novel synergizing agents can be readily identified using this assay. The assay involves isolating human tonsillar B cells by magnetic bead (MACS) depletion of CD3-positive cells. The resulting cell population is greater than 95% B cells as assessed by expression of CD45R(B220).

[0944] Various dilutions of each sample are placed into individual wells of a 96-well plate to which are added 10^5 B-cells suspended in culture medium (RPMI 1640 containing 10% FBS, 5 X 10^{-5}M 2ME, 100U/ml penicillin, 10ug/ml streptomycin, and 10^{-5} dilution of SAC) in a total volume of 150ul. Proliferation or inhibition is quantitated by a 20h pulse (1uCi/well) with 3H-thymidine (6.7 Ci/mM) beginning 72h post factor addition. The positive and negative controls are IL2 and medium respectively.

[0945] **In Vivo Assay**- BALB/c mice are injected (i.p.) twice per day with buffer only, or 2 mg/Kg of agonists or antagonists of the invention, or truncated forms thereof. Mice receive this treatment for 4 consecutive days, at which time they are sacrificed and various tissues and serum collected for analyses. Comparison of H&E sections from normal spleens and spleens treated with agonists or antagonists of the invention identify the results of the activity of the agonists or antagonists on spleen cells, such as the

diffusion of peri-arterial lymphatic sheaths, and/or significant increases in the nucleated cellularity of the red pulp regions, which may indicate the activation of the differentiation and proliferation of B-cell populations. Immunohistochemical studies using a B cell marker, anti-CD45R(B220), are used to determine whether any physiological changes to splenic cells, such as splenic disorganization, are due to increased B-cell representation within loosely defined B-cell zones that infiltrate established T-cell regions.

[0946] Flow cytometric analyses of the spleens from mice treated with agonist or antagonist is used to indicate whether the agonists or antagonists specifically increases the proportion of ThB+, CD45R(B220)dull B cells over that which is observed in control mice.

Likewise, a predicted consequence of increased mature B-cell representation in vivo is a relative increase in serum Ig titers. Accordingly, serum IgM and IgA levels are compared between buffer and agonists or antagonists-treated mice.

[0947] The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 22: T Cell Proliferation Assay

[0948] A CD3-induced proliferation assay is performed on PBMCs and is measured by the uptake of ^{3}H-thymidine. The assay is performed as follows. Ninety-six well plates are coated with 100 μl/well of mAb to CD3 (HIT3a, Pharmingen) or isotype-matched control mAb (B33.1) overnight at 4 degrees C (1 μg/ml in .05M bicarbonate buffer, pH 9.5), then washed three times with PBS. PBMC are isolated by F/H gradient centrifugation from human peripheral blood and added to quadruplicate wells (5 x 10^4/well) of mAb coated plates in RPMI containing 10% FCS and P/S in the presence of varying concentrations of agonists or antagonists of the invention (total volume 200 ul). Relevant protein buffer and medium alone are controls. After 48 hr. culture at 37 degrees C, plates are spun for 2 min. at 1000 rpm and 100 μl of supernatant is removed and stored –20 degrees C for measurement of IL-2 (or other cytokines) if effect on proliferation is observed. Wells are supplemented with 100 ul of medium containing 0.5 uCi of ^{3}H-

thymidine and cultured at 37 degrees C for 18-24 hr. Wells are harvested and incorporation of ^{3}H-thymidine used as a measure of proliferation. Anti-CD3 alone is the positive control for proliferation. IL-2 (100 U/ml) is also used as a control which enhances proliferation. Control antibody which does not induce proliferation of T cells is used as the negative controls for the effects of agonists or antagonists of the invention.

[0949] The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 23: Effect of Agonists or Antagonists of the Invention on the Expression of MHC Class II, Costimulatory and Adhesion Molecules and Cell Differentiation of Monocytes and Monocyte-Derived Human Dendritic Cells

[0950] Dendritic cells are generated by the expansion of proliferating precursors found in the peripheral blood: adherent PBMC or elutriated monocytic fractions are cultured for 7-10 days with GM-CSF (50 ng/ml) and IL-4 (20 ng/ml). These dendritic cells have the characteristic phenotype of immature cells (expression of CD1, CD80, CD86, CD40 and MHC class II antigens). Treatment with activating factors, such as TNF-α, causes a rapid change in surface phenotype (increased expression of MHC class I and II, costimulatory and adhesion molecules, downregulation of FCγRII, upregulation of CD83). These changes correlate with increased antigen-presenting capacity and with functional maturation of the dendritic cells.

[0951] FACS analysis of surface antigens is performed as follows. Cells are treated 1-3 days with increasing concentrations of agonist or antagonist of the invention or LPS (positive control), washed with PBS containing 1% BSA and 0.02 mM sodium azide, and then incubated with 1:20 dilution of appropriate FITC- or PE-labeled monoclonal antibodies for 30 minutes at 4 degrees C. After an additional wash, the labeled cells are analyzed by flow cytometry on a FACScan (Becton Dickinson).

[0952] <u>Effect on the production of cytokines</u>. Cytokines generated by dendritic cells, in particular IL-12, are important in the initiation of T-cell dependent immune

responses. IL-12 strongly influences the development of Thl helper T-cell immune response, and induces cytotoxic T and NK cell function. An ELISA is used to measure the IL-12 release as follows. Dendritic cells (10^6/ml) are treated with increasing concentrations of agonists or antagonists of the invention for 24 hours. LPS (100 ng/ml) is added to the cell culture as positive control. Supernatants from the cell cultures are then collected and analyzed for IL-12 content using commercial ELISA kit (e..g, R & D Systems (Minneapolis, MN)). The standard protocols provided with the kits are used.

[0953] Effect on the expression of MHC Class II, costimulatory and adhesion molecules. Three major families of cell surface antigens can be identified on monocytes: adhesion molecules, molecules involved in antigen presentation, and Fc receptor. Modulation of the expression of MHC class II antigens and other costimulatory molecules, such as B7 and ICAM-1, may result in changes in the antigen presenting capacity of monocytes and ability to induce T cell activation. Increase expression of Fc receptors may correlate with improved monocyte cytotoxic activity, cytokine release and phagocytosis.

[0954] FACS analysis is used to examine the surface antigens as follows. Monocytes are treated 1-5 days with increasing concentrations of agonists or antagonists of the invention or LPS (positive control), washed with PBS containing 1% BSA and 0.02 mM sodium azide, and then incubated with 1:20 dilution of appropriate FITC- or PE-labeled monoclonal antibodies for 30 minutes at 4 degreesC. After an additional wash, the labeled cells are analyzed by flow cytometry on a FACScan (Becton Dickinson).

[0955] Monocyte activation and/or increased survival. Assays for molecules that activate (or alternatively, inactivate) monocytes and/or increase monocyte survival (or alternatively, decrease monocyte survival) are known in the art and may routinely be applied to determine whether a molecule of the invention functions as an inhibitor or activator of monocytes. Agonists or antagonists of the invention can be screened using the three assays described below. For each of these assays, Peripheral blood mononuclear cells (PBMC) are purified from single donor leukopacks (American Red Cross, Baltimore, MD) by centrifugation through a Histopaque gradient (Sigma). Monocytes are isolated from PBMC by counterflow centrifugal elutriation.

[0956] Monocyte Survival Assay. Human peripheral blood monocytes progressively lose viability when cultured in absence of serum or other stimuli. Their death results from internally regulated process (apoptosis). Addition to the culture of activating factors, such as TNF-alpha dramatically improves cell survival and prevents DNA fragmentation. Propidium iodide (PI) staining is used to measure apoptosis as follows. Monocytes are cultured for 48 hours in polypropylene tubes in serum-free medium (positive control), in the presence of 100 ng/ml TNF-alpha (negative control), and in the presence of varying concentrations of the compound to be tested. Cells are suspended at a concentration of 2 x 10^6/ml in PBS containing PI at a final concentration of 5 μg/ml, and then incubaed at room temperature for 5 minutes before FACScan analysis. PI uptake has been demonstrated to correlate with DNA fragmentation in this experimental paradigm.

[0957] Effect on cytokine release. An important function of monocytes/macrophages is their regulatory activity on other cellular populations of the immune system through the release of cytokines after stimulation. An ELISA to measure cytokine release is performed as follows. Human monocytes are incubated at a density of $5x10^5$ cells/ml with increasing concentrations of agonists or antagonists of the invention and under the same conditions, but in the absence of agonists or antagonists. For IL-12 production, the cells are primed overnight with IFN (100 U/ml) in presence of agonist or antagonist of the invention. LPS (10 ng/ml) is then added. Conditioned media are collected after 24h and kept frozen until use. Measurement of TNF-alpha, IL-10, MCP-1 and IL-8 is then performed using a commercially available ELISA kit (e. g, R & D Systems (Minneapolis, MN)) and applying the standard protocols provided with the kit.

[0958] Oxidative burst. Purified monocytes are plated in 96-w plate at $2\text{-}1x10^5$ cell/well. Increasing concentrations of agonists or antagonists of the invention are added to the wells in a total volume of 0.2 ml culture medium (RPMI 1640 + 10% FCS, glutamine and antibiotics). After 3 days incubation, the plates are centrifuged and the medium is removed from the wells. To the macrophage monolayers, 0.2 ml per well of phenol red solution (140 mM NaCl, 10 mM potassium phosphate buffer pH 7.0, 5.5 mM dextrose, 0.56 mM phenol red and 19 U/ml of HRPO) is added, together with the stimulant (200 nM

PMA). The plates are incubated at 37°C for 2 hours and the reaction is stopped by adding 20 μl 1N NaOH per well. The absorbance is read at 610 nm. To calculate the amount of H_2O_2 produced by the macrophages, a standard curve of a H_2O_2 solution of known molarity is performed for each experiment.

[0959] The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 24: Biological Effects of Agonists or Antagonists of the Invention

Astrocyte and Neuronal Assays.

[0960] Agonists or antagonists of the invention, expressed in *Escherichia coli* and purified as described above, can be tested for activity in promoting the survival, neurite outgrowth, or phenotypic differentiation of cortical neuronal cells and for inducing the proliferation of glial fibrillary acidic protein immunopositive cells, astrocytes. The selection of cortical cells for the bioassay is based on the prevalent expression of FGF-1 and FGF-2 in cortical structures and on the previously reported enhancement of cortical neuronal survival resulting from FGF-2 treatment. A thymidine incorporation assay, for example, can be used to elucidate an agonist or antagonist of the invention's activity on these cells.

[0961] Moreover, previous reports describing the biological effects of FGF-2 (basic FGF) on cortical or hippocampal neurons *in vitro* have demonstrated increases in both neuron survival and neurite outgrowth (Walicke et al., "Fibroblast growth factor promotes survival of dissociated hippocampal neurons and enhances neurite extension." *Proc. Natl. Acad. Sci. USA 83*:3012-3016. (1986), assay herein incorporated by reference in its entirety). However, reports from experiments done on PC-12 cells suggest that these two responses are not necessarily synonymous and may depend on not only which FGF is being tested but also on which receptor(s) are expressed on the target cells. Using the primary cortical neuronal culture paradigm, the ability of an agonist or antagonist of the

invention to induce neurite outgrowth can be compared to the response achieved with FGF-2 using, for example, a thymidine incorporation assay.

Fibroblast and endothelial cell assays.

[0962] Human lung fibroblasts are obtained from Clonetics (San Diego, CA) and maintained in growth media from Clonetics. Dermal microvascular endothelial cells are obtained from Cell Applications (San Diego, CA). For proliferation assays, the human lung fibroblasts and dermal microvascular endothelial cells can be cultured at 5,000 cells/well in a 96-well plate for one day in growth medium. The cells are then incubated for one day in 0.1% BSA basal medium. After replacing the medium with fresh 0.1% BSA medium, the cells are incubated with the test proteins for 3 days. Alamar Blue (Alamar Biosciences, Sacramento, CA) is added to each well to a final concentration of 10%. The cells are incubated for 4 hr. Cell viability is measured by reading in a CytoFluor fluorescence reader. For the PGE_2 assays, the human lung fibroblasts are cultured at 5,000 cells/well in a 96-well plate for one day. After a medium change to 0.1% BSA basal medium, the cells are incubated with FGF-2 or agonists or antagonists of the invention with or without IL-1α for 24 hours. The supernatants are collected and assayed for PGE_2 by EIA kit (Cayman, Ann Arbor, MI). For the IL-6 assays, the human lung fibroblasts are cultured at 5,000 cells/well in a 96-well plate for one day. After a medium change to 0.1% BSA basal medium, the cells are incubated with FGF-2 or with or without agonists or antagonists of the invention IL-1α for 24 hours. The supernatants are collected and assayed for IL-6 by ELISA kit (Endogen, Cambridge, MA).

[0963] Human lung fibroblasts are cultured with FGF-2 or agonists or antagonists of the invention for 3 days in basal medium before the addition of Alamar Blue to assess effects on growth of the fibroblasts. FGF-2 should show a stimulation at 10 - 2500 ng/ml which can be used to compare stimulation with agonists or antagonists of the invention.

Parkinson Models.

[0964] The loss of motor function in Parkinson's disease is attributed to a deficiency of striatal dopamine resulting from the degeneration of the nigrostriatal

dopaminergic projection neurons. An animal model for Parkinson's that has been extensively characterized involves the systemic administration of 1-methyl-4 phenyl 1,2,3,6-tetrahydropyridine (MPTP). In the CNS, MPTP is taken-up by astrocytes and catabolized by monoamine oxidase B to 1-methyl-4-phenyl pyridine (MPP^+) and released. Subsequently, MPP^+ is actively accumulated in dopaminergic neurons by the high-affinity reuptake transporter for dopamine. MPP^+ is then concentrated in mitochondria by the electrochemical gradient and selectively inhibits nicotidamide adenine disphosphate: ubiquinone oxidoreductionase (complex I), thereby interfering with electron transport and eventually generating oxygen radicals.

[0965] It has been demonstrated in tissue culture paradigms that FGF-2 (basic FGF) has trophic activity towards nigral dopaminergic neurons (Ferrari et al., Dev. Biol. 1989). Recently, Dr. Unsicker's group has demonstrated that administering FGF-2 in gel foam implants in the striatum results in the near complete protection of nigral dopaminergic neurons from the toxicity associated with MPTP exposure (Otto and Unsicker, J. Neuroscience, 1990).

[0966] Based on the data with FGF-2, agonists or antagonists of the invention can be evaluated to determine whether it has an action similar to that of FGF-2 in enhancing dopaminergic neuronal survival *in vitro* and it can also be tested *in vivo* for protection of dopaminergic neurons in the striatum from the damage associated with MPTP treatment. The potential effect of an agonist or antagonist of the invention is first examined in vitro in a dopaminergic neuronal cell culture paradigm. The cultures are prepared by dissecting the midbrain floor plate from gestation day 14 Wistar rat embryos. The tissue is dissociated with trypsin and seeded at a density of 200,000 cells/cm^2 on polyorthinine-laminin coated glass coverslips. The cells are maintained in Dulbecco's Modified Eagle's medium and F12 medium containing hormonal supplements (N1). The cultures are fixed with paraformaldehyde after 8 days in vitro and are processed for tyrosine hydroxylase, a specific marker for dopminergic neurons, immunohistochemical staining. Dissociated cell cultures are prepared from embryonic rats. The culture medium is changed every third day and the factors are also added at that time.

[0967] Since the dopaminergic neurons are isolated from animals at gestation day 14, a developmental time which is past the stage when the dopaminergic precursor cells are proliferating, an increase in the number of tyrosine hydroxylase immunopositive

neurons would represent an increase in the number of dopaminergic neurons surviving *in vitro*. Therefore, if an agonist or antagonist of the invention acts to prolong the survival of dopaminergic neurons, it would suggest that the agonist or antagonist may be involved in Parkinson's Disease.

[0968] The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 25: The Effect of Agonists or Antagonists of the Invention on the Growth of Vascular Endothelial Cells

[0969] On day 1, human umbilical vein endothelial cells (HUVEC) are seeded at 2-5x10^4 cells/35 mm dish density in M199 medium containing 4% fetal bovine serum (FBS), 16 units/ml heparin, and 50 units/ml endothelial cell growth supplements (ECGS, Biotechnique, Inc.). On day 2, the medium is replaced with M199 containing 10% FBS, 8 units/ml heparin. An agonist or antagonist of the invention, and positive controls, such as VEGF and basic FGF (bFGF) are added, at varying concentrations. On days 4 and 6, the medium is replaced. On day 8, cell number is determined with a Coulter Counter.

[0970] An increase in the number of HUVEC cells indicates that the compound of the invention may proliferate vascular endothelial cells, while a decrease in the number of HUVEC cell indicates that the compound of the invention inhibits vascular endothelial cells.

[0971] The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 26: Rat Corneal Wound Healing Model

[0972] This animal model shows the effect of an agonist or antagonist of the

invention on neovascularization. The experimental protocol includes:

a) Making a 1-1.5 mm long incision from the center of cornea into the stromal layer.

b) Inserting a spatula below the lip of the incision facing the outer corner of the eye.

c) Making a pocket (its base is 1-1.5 mm form the edge of the eye).

d) Positioning a pellet, containing 50ng- 5ug of an agonist or antagonist of the invention, within the pocket.

e) Treatment with an agonist or antagonist of the invention can also be applied topically to the corneal wounds in a dosage range of 20mg - 500mg (daily treatment for five days).

[0973] The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 27: Diabetic Mouse and Glucocorticoid-Impaired Wound Healing Models

A. Diabetic db+/db+ Mouse Model.

[0974] To demonstrate that an agonist or antagonist of the invention accelerates the healing process, the genetically diabetic mouse model of wound healing is used. The full thickness wound healing model in the db+/db+ mouse is a well characterized, clinically relevant and reproducible model of impaired wound healing. Healing of the diabetic wound is dependent on formation of granulation tissue and re-epithelialization rather than contraction (Gartner, M.H. *et al., J. Surg. Res. 52*:389 (1992); Greenhalgh, D.G. *et al., Am. J. Pathol. 136*:1235 (1990)).

[0975] The diabetic animals have many of the characteristic features observed in Type II diabetes mellitus. Homozygous (db+/db+) mice are obese in comparison to their normal heterozygous (db+/+m) littermates. Mutant diabetic (db+/db+) mice have a single autosomal recessive mutation on chromosome 4 (db+) (Coleman *et al. Proc. Natl. Acad. Sci. USA 77*:283-293 (1982)). Animals show polyphagia, polydipsia and polyuria. Mutant diabetic mice (db+/db+) have elevated blood glucose, increased or normal insulin

levels, and suppressed cell-mediated immunity (Mandel *et al., J. Immunol. 120*:1375 (1978); Debray-Sachs, M. *et al., Clin. Exp. Immunol. 51(1)*:1-7 (1983); Leiter *et al., Am. J. of Pathol. 114*:46-55 (1985)). Peripheral neuropathy, myocardial complications, and microvascular lesions, basement membrane thickening and glomerular filtration abnormalities have been described in these animals (Norido, F. *et al., Exp. Neurol. 83(2)*:221-232 (1984); Robertson *et al., Diabetes 29(1)*:60-67 (1980); Giacomelli *et al., Lab Invest. 40(4)*:460-473 (1979); Coleman, D.L., *Diabetes 31 (Suppl)*:1-6 (1982)). These homozygous diabetic mice develop hyperglycemia that is resistant to insulin analogous to human type II diabetes (Mandel *et al., J. Immunol. 120*:1375-1377 (1978)).

[0976] The characteristics observed in these animals suggests that healing in this model may be similar to the healing observed in human diabetes (Greenhalgh, *et al., Am. J. of Pathol. 136*:1235-1246 (1990)).

[0977] Genetically diabetic female C57BL/KsJ (db+/db+) mice and their non-diabetic (db+/+m) heterozygous littermates are used in this study (Jackson Laboratories). The animals are purchased at 6 weeks of age and are 8 weeks old at the beginning of the study. Animals are individually housed and received food and water ad libitum. All manipulations are performed using aseptic techniques. The experiments are conducted according to the rules and guidelines of Human Genome Sciences, Inc. Institutional Animal Care and Use Committee and the Guidelines for the Care and Use of Laboratory Animals.

[0978] Wounding protocol is performed according to previously reported methods (Tsuboi, R. and Rifkin, D.B., *J. Exp. Med. 172*:245-251 (1990)). Briefly, on the day of wounding, animals are anesthetized with an intraperitoneal injection of Avertin (0.01 mg/mL), 2,2,2-tribromoethanol and 2-methyl-2-butanol dissolved in deionized water. The dorsal region of the animal is shaved and the skin washed with 70% ethanol solution and iodine. The surgical area is dried with sterile gauze prior to wounding. An 8 mm full-thickness wound is then created using a Keyes tissue punch. Immediately following wounding, the surrounding skin is gently stretched to eliminate wound expansion. The wounds are left open for the duration of the experiment. Application of the treatment is given topically for 5 consecutive days commencing on the day of wounding. Prior to treatment, wounds are gently cleansed with sterile saline and gauze sponges.

[0979] Wounds are visually examined and photographed at a fixed distance at the

day of surgery and at two day intervals thereafter. Wound closure is determined by daily measurement on days 1-5 and on day 8. Wounds are measured horizontally and vertically using a calibrated Jameson caliper. Wounds are considered healed if granulation tissue is no longer visible and the wound is covered by a continuous epithelium.

[0980] An agonist or antagonist of the invention is administered using at a range different doses, from 4mg to 500mg per wound per day for 8 days in vehicle. Vehicle control groups received 50mL of vehicle solution.

[0981] Animals are euthanized on day 8 with an intraperitoneal injection of sodium pentobarbital (300mg/kg). The wounds and surrounding skin are then harvested for histology and immunohistochemistry. Tissue specimens are placed in 10% neutral buffered formalin in tissue cassettes between biopsy sponges for further processing.

Three groups of 10 animals each (5 diabetic and 5 non-diabetic controls) are evaluated: 1) Vehicle placebo control, 2) untreated group, and 3) treated group.

Wound closure is analyzed by measuring the area in the vertical and horizontal axis and obtaining the total square area of the wound. Contraction is then estimated by establishing the differences between the initial wound area (day 0) and that of post treatment (day 8). The wound area on day 1 is $64mm^2$, the corresponding size of the dermal punch. Calculations are made using the following formula:

[Open area on day 8] - [Open area on day 1] / [Open area on day 1]

Specimens are fixed in 10% buffered formalin and paraffin embedded blocks are sectioned perpendicular to the wound surface (5mm) and cut using a Reichert-Jung microtome. Routine hematoxylin-eosin (H&E) staining is performed on cross-sections of bisected wounds. Histologic examination of the wounds are used to assess whether the healing process and the morphologic appearance of the repaired skin is altered by treatment with an agonist or antagonist of the invention. This assessment included verification of the presence of cell accumulation, inflammatory cells, capillaries, fibroblasts, re-epithelialization and epidermal maturity (Greenhalgh, D.G. *et al., Am. J. Pathol. 136:*1235 (1990)). A calibrated lens micrometer is used by a blinded observer.

[0982] Tissue sections are also stained immunohistochemically with a polyclonal rabbit anti-human keratin antibody using ABC Elite detection system. Human skin is used

as a positive tissue control while non-immune IgG is used as a negative control. Keratinocyte growth is determined by evaluating the extent of reepithelialization of the wound using a calibrated lens micrometer.

[0983] Proliferating cell nuclear antigen/cyclin (PCNA) in skin specimens is demonstrated by using anti-PCNA antibody (1:50) with an ABC Elite detection system. Human colon cancer served as a positive tissue control and human brain tissue is used as a negative tissue control. Each specimen included a section with omission of the primary antibody and substitution with non-immune mouse IgG. Ranking of these sections is based on the extent of proliferation on a scale of 0-8, the lower side of the scale reflecting slight proliferation to the higher side reflecting intense proliferation.

[0984] Experimental data are analyzed using an unpaired t test. A p value of < 0.05 is considered significant.

B. Steroid Impaired Rat Model

[0985] The inhibition of wound healing by steroids has been well documented in various *in vitro* and *in vivo* systems (Wahl, Glucocorticoids and Wound healing. In: Anti-Inflammatory Steroid Action: Basic and Clinical Aspects. 280-302 (1989); Wahl*et al., J. Immunol. 115*: 476-481 (1975); Werb *et al., J. Exp. Med. 147*:1684-1694 (1978)). Glucocorticoids retard wound healing by inhibiting angiogenesis, decreasing vascular permeability (Ebert *et al., An. Intern. Med. 37*:701-705 (1952)), fibroblast proliferation, and collagen synthesis (Beck *et al., Growth Factors. 5:* 295-304 (1991); Haynes *et al., J. Clin. Invest. 61:* 703-797 (1978)) and producing a transient reduction of circulating monocytes (Haynes et al., *J. Clin. Invest. 61:* 703-797 (1978); Wahl, "Glucocorticoids and wound healing", *In:* Antiinflammatory Steroid Action: Basic and Clinical Aspects, Academic Press, New York, pp. 280-302 (1989)). The systemic administration of steroids to impaired wound healing is a well establish phenomenon in rats (Beck *et al., Growth Factors. 5:* 295-304 (1991); Haynes *et al., J. Clin. Invest. 61:* 703-797 (1978); Wahl, "Glucocorticoids and wound healing", *In*: Antiinflammatory Steroid Action: Basic and Clinical Aspects, Academic Press, New York, pp. 280-302 (1989); Pierce *et al., Proc. Natl. Acad. Sci. USA 86*: 2229-2233 (1989)).

[0986] To demonstrate that an agonist or antagonist of the invention can accelerate the healing process, the effects of multiple topical applications of the agonist or

antagonist on full thickness excisional skin wounds in rats in which healing has been impaired by the systemic administration of methylprednisolone is assessed.

[0987] Young adult male Sprague Dawley rats weighing 250-300 g (Charles River Laboratories) are used in this example. The animals are purchased at 8 weeks of age and are 9 weeks old at the beginning of the study. The healing response of rats is impaired by the systemic administration of methylprednisolone (17mg/kg/rat intramuscularly) at the time of wounding. Animals are individually housed and received food and water *ad libitum*. All manipulations are performed using aseptic techniques. This study is conducted according to the rules and guidelines of Human Genome Sciences, Inc. Institutional Animal Care and Use Committee and the Guidelines for the Care and Use of Laboratory Animals.

[0988] The wounding protocol is followed according to section A, above. On the day of wounding, animals are anesthetized with an intramuscular injection of ketamine (50 mg/kg) and xylazine (5 mg/kg). The dorsal region of the animal is shaved and the skin washed with 70% ethanol and iodine solutions. The surgical area is dried with sterile gauze prior to wounding. An 8 mm full-thickness wound is created using a Keyes tissue punch. The wounds are left open for the duration of the experiment. Applications of the testing materials are given topically once a day for 7 consecutive days commencing on the day of wounding and subsequent to methylprednisolone administration. Prior to treatment, wounds are gently cleansed with sterile saline and gauze sponges.

[0989] Wounds are visually examined and photographed at a fixed distance at the day of wounding and at the end of treatment. Wound closure is determined by daily measurement on days 1-5 and on day 8. Wounds are measured horizontally and vertically using a calibrated Jameson caliper. Wounds are considered healed if granulation tissue is no longer visible and the wound is covered by a continuous epithelium.

[0990] The agonist or antagonist of the invention is administered using at a range different doses, from 4mg to 500mg per wound per day for 8 days in vehicle. Vehicle control groups received 50mL of vehicle solution.

[0991] Animals are euthanized on day 8 with an intraperitoneal injection of sodium pentobarbital (300mg/kg). The wounds and surrounding skin are then harvested for histology. Tissue specimens are placed in 10% neutral buffered formalin in tissue cassettes between biopsy sponges for further processing.

[0992] Four groups of 10 animals each (5 with methylprednisolone and 5 without glucocorticoid) are evaluated: 1) Untreated group 2) Vehicle placebo control 3) treated groups.

[0993] Wound closure is analyzed by measuring the area in the vertical and horizontal axis and obtaining the total area of the wound. Closure is then estimated by establishing the differences between the initial wound area (day 0) and that of post treatment (day 8). The wound area on day 1 is $64mm^2$, the corresponding size of the dermal punch. Calculations are made using the following formula:

[Open area on day 8] - [Open area on day 1] / [Open area on day 1]

Specimens are fixed in 10% buffered formalin and paraffin embedded blocks are sectioned perpendicular to the wound surface (5mm) and cut using an Olympus microtome. Routine hematoxylin-eosin (H&E) staining is performed on cross-sections of bisected wounds. Histologic examination of the wounds allows assessment of whether the healing process and the morphologic appearance of the repaired skin is improved by treatment with an agonist or antagonist of the invention. A calibrated lens micrometer is used by a blinded observer to determine the distance of the wound gap.

[0994] Experimental data are analyzed using an unpaired t test. A p value of < 0.05 is considered significant

[0995] The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 28: Lymphadema Animal Model

[0996] The purpose of this experimental approach is to create an appropriate and consistent lymphedema model for testing the therapeutic effects of an agonist or antagonist of the invention in lymphangiogenesis and re-establishment of the lymphatic circulatory system in the rat hind limb. Effectiveness is measured by swelling volume of the affected limb, quantification of the amount of lymphatic vasculature, total blood

plasma protein, and histopathology. Acute lymphedema is observed for 7-10 days. Perhaps more importantly, the chronic progress of the edema is followed for up to 3-4 weeks.

[0997] Prior to beginning surgery, blood sample is drawn for protein concentration analysis. Male rats weighing approximately ~350g are dosed with Pentobarbital. Subsequently, the right legs are shaved from knee to hip. The shaved area is swabbed with gauze soaked in 70% EtOH. Blood is drawn for serum total protein testing. Circumference and volumetric measurements are made prior to injecting dye into paws after marking 2 measurement levels (0.5 cm above heel, at mid-pt of dorsal paw). The intradermal dorsum of both right and left paws are injected with 0.05 ml of 1% Evan's Blue. Circumference and volumetric measurements are then made following injection of dye into paws.

[0998] Using the knee joint as a landmark, a mid-leg inguinal incision is made circumferentially allowing the femoral vessels to be located. Forceps and hemostats are used to dissect and separate the skin flaps. After locating the femoral vessels, the lymphatic vessel that runs along side and underneath the vessel(s) is located. The main lymphatic vessels in this area are then electrically coagulated or suture ligated.

[0999] Using a microscope, muscles in back of the leg (near the semitendinosis and adductors) are bluntly dissected. The popliteal lymph node is then located. The 2 proximal and 2 distal lymphatic vessels and distal blood supply of the popliteal node are then and ligated by suturing. The popliteal lymph node, and any accompanying adipose tissue, is then removed by cutting connective tissues.

[1000] Care is taken to control any mild bleeding resulting from this procedure. After lymphatics are occluded, the skin flaps are sealed by using liquid skin (Vetbond) (AJ Buck). The separated skin edges are sealed to the underlying muscle tissue while leaving a gap of ~0.5 cm around the leg. Skin also may be anchored by suturing to underlying muscle when necessary.

[1001] To avoid infection, animals are housed individually with mesh (no bedding). Recovering animals are checked daily through the optimal edematous peak, which typically occurred by day 5-7. The plateau edematous peak are then observed. To evaluate the intensity of the lymphedema, the circumference and volumes of 2 designated places on each paw before operation and daily for 7 days are measured. The effect plasma

proteins on lymphedema is determined and whether protein analysis is a useful testing perimeter is also investigated. The weights of both control and edematous limbs are evaluated at 2 places. Analysis is performed in a blind manner.

[1002] Circumference Measurements: Under brief gas anesthetic to prevent limb movement, a cloth tape is used to measure limb circumference. Measurements are done at the ankle bone and dorsal paw by 2 different people then those 2 readings are averaged. Readings are taken from both control and edematous limbs.

[1003] Volumetric Measurements: On the day of surgery, animals are anesthetized with Pentobarbital and are tested prior to surgery. For daily volumetrics animals are under brief halothane anesthetic (rapid immobilization and quick recovery), both legs are shaved and equally marked using waterproof marker on legs. Legs are first dipped in water, then dipped into instrument to each marked level then measured by Buxco edema software(Chen/Victor). Data is recorded by one person, while the other is dipping the limb to marked area.

[1004] Blood-plasma protein measurements: Blood is drawn, spun, and serum separated prior to surgery and then at conclusion for total protein and Ca2+ comparison.

[1005] Limb Weight Comparison: After drawing blood, the animal is prepared for tissue collection. The limbs are amputated using a quillitine, then both experimental and control legs are cut at the ligature and weighed. A second weighing is done as the tibio-cacaneal joint is disarticulated and the foot is weighed.

[1006] Histological Preparations: The transverse muscle located behind the knee (popliteal) area is dissected and arranged in a metal mold, filled with freezeGel, dipped into cold methylbutane, placed into labeled sample bags at - 80EC until sectioning. Upon sectioning, the muscle is observed under fluorescent microscopy for lymphatics.

[1007] The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 29: Suppression of TNF alpha-induced adhesion molecule expression by a Agonist or Antagonist of the Invention

[1008] The recruitment of lymphocytes to areas of inflammation and angiogenesis involves specific receptor-ligand interactions between cell surface adhesion molecules (CAMs) on lymphocytes and the vascular endothelium. The adhesion process, in both normal and pathological settings, follows a multi-step cascade that involves intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial leukocyte adhesion molecule-1 (E-selectin) expression on endothelial cells (EC). The expression of these molecules and others on the vascular endothelium determines the efficiency with which leukocytes may adhere to the local vasculature and extravasate into the local tissue during the development of an inflammatory response. The local concentration of cytokines and growth factor participate in the modulation of the expression of these CAMs.

[1009] Tumor necrosis factor alpha (TNF-a), a potent proinflammatory cytokine, is a stimulator of all three CAMs on endothelial cells and may be involved in a wide variety of inflammatory responses, often resulting in a pathological outcome.

[1010] The potential of an agonist or antagonist of the invention to mediate a suppression of TNF-a induced CAM expression can be examined. A modified ELISA assay which uses ECs as a solid phase absorbent is employed to measure the amount of CAM expression on TNF-a treated ECs when co-stimulated with a member of the FGF family of proteins.

[1011] To perform the experiment, human umbilical vein endothelial cell (HUVEC) cultures are obtained from pooled cord harvests and maintained in growth medium (EGM-2; Clonetics, San Diego, CA) supplemented with 10% FCS and 1% penicillin/streptomycin in a 37 degree C humidified incubator containing 5% CO_2. HUVECs are seeded in 96-well plates at concentrations of 1 x 10^4 cells/well in EGM medium at 37 degree C for 18-24 hrs or until confluent. The monolayers are subsequently washed 3 times with a serum-free solution of RPMI-1640 supplemented with 100 U/ml penicillin and 100 mg/ml streptomycin, and treated with a given cytokine and/or growth factor(s) for 24 h at 37 degree C. Following incubation, the cells are then evaluated for CAM expression.

[1012] Human Umbilical Vein Endothelial cells (HUVECs) are grown in a standard 96 well plate to confluence. Growth medium is removed from the cells and replaced with 90 ul of 199 Medium (10% FBS). Samples for testing and positive or

negative controls are added to the plate in triplicate (in 10 ul volumes). Plates are incubated at 37 degree C for either 5 h (selectin and integrin expression) or 24 h (integrin expression only). Plates are aspirated to remove medium and 100 μl of 0.1% paraformaldehyde-PBS(with Ca++ and Mg++) is added to each well. Plates are held at 4°C for 30 min.

[1013] Fixative is then removed from the wells and wells are washed 1X with PBS(+Ca,Mg)+0.5% BSA and drained. Do not allow the wells to dry. Add 10 μl of diluted primary antibody to the test and control wells. Anti-ICAM-1-Biotin, Anti-VCAM-1-Biotin and Anti-E-selectin-Biotin are used at a concentration of 10 μg/ml (1:10 dilution of 0.1 mg/ml stock antibody). Cells are incubated at 37°C for 30 min. in a humidified environment. Wells are washed X3 with PBS(+Ca,Mg)+0.5% BSA.

[1014] Then add 20 μl of diluted ExtrAvidin-Alkaline Phosphotase (1:5,000 dilution) to each well and incubated at 37°C for 30 min. Wells are washed X3 with PBS(+Ca,Mg)+0.5% BSA. 1 tablet of p-Nitrophenol Phosphate pNPP is dissolved in 5 ml of glycine buffer (pH 10.4). 100 μl of pNPP substrate in glycine buffer is added to each test well. Standard wells in triplicate are prepared from the working dilution of the ExtrAvidin-Alkaline Phosphotase in glycine buffer: 1:5,000 (10^0) > $10^{-0.5}$ > 10^{-1} > $10^{-1.5}$. 5 μl of each dilution is added to triplicate wells and the resulting AP content in each well is 5.50 ng, 1.74 ng, 0.55 ng, 0.18 ng. 100 μl of pNNP reagent must then be added to each of the standard wells. The plate must be incubated at 37°C for 4h. A volume of 50 μl of 3M NaOH is added to all wells. The results are quantified on a plate reader at 405 nm. The background subtraction option is used on blank wells filled with glycine buffer only. The template is set up to indicate the concentration of AP-conjugate in each standard well [5.50 ng; 1.74 ng; 0.55 ng; 0.18 ng]. Results are indicated as amount of bound AP-conjugate in each sample.

[1015] The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 30: Production Of Polypeptide of the Invention For High-Throughput Screening Assays

[1016] The following protocol produces a supernatant containing polypeptide of the present invention to be tested. This supernatant can then be used in the Screening Assays described in Examples 32-41.

[1017] First, dilute Poly-D-Lysine (644 587 Boehringer-Mannheim) stock solution (1mg/ml in PBS) 1:20 in PBS (w/o calcium or magnesium 17-516F Biowhittaker) for a working solution of 50ug/ml. Add 200 ul of this solution to each well (24 well plates) and incubate at RT for 20 minutes. Be sure to distribute the solution over each well (note: a 12-channel pipetter may be used with tips on every other channel). Aspirate off the Poly-D-Lysine solution and rinse with 1ml PBS (Phosphate Buffered Saline). The PBS should remain in the well until just prior to plating the cells and plates may be poly-lysine coated in advance for up to two weeks.

[1018] Plate 293T cells (do not carry cells past P+20) at 2 x 10^5 cells/well in .5ml DMEM(Dulbecco's Modified Eagle Medium)(with 4.5 G/L glucose and L-glutamine (12-604F Biowhittaker))/10% heat inactivated FBS(14-503F Biowhittaker)/1x Penstrep(17-602E Biowhittaker). Let the cells grow overnight.

[1019] The next day, mix together in a sterile solution basin: 300 ul Lipofectamine (18324-012 Gibco/BRL) and 5ml Optimem I (31985070 Gibco/BRL)/96-well plate. With a small volume multi-channel pipetter, aliquot approximately 2ug of an expression vector containing a polynucleotide insert, produced by the methods described in Examples 8-10, into an appropriately labeled 96-well round bottom plate. With a multi-channel pipetter, add 50ul of the Lipofectamine/Optimem I mixture to each well. Pipette up and down gently to mix. Incubate at RT 15-45 minutes. After about 20 minutes, use a multi-channel pipetter to add 150ul Optimem I to each well. As a control, one plate of vector DNA lacking an insert should be transfected with each set of transfections.

[1020] Preferably, the transfection should be performed by tag-teaming the following tasks. By tag-teaming, hands on time is cut in half, and the cells do not spend too much time on PBS. First, person A aspirates off the media from four 24-well plates of cells, and then person B rinses each well with .5-1ml PBS. Person A then aspirates off PBS rinse, and person B, using a12-channel pipetter with tips on every other channel, adds the 200ul of DNA/Lipofectamine/Optimem I complex to the odd wells first, then to the even wells, to each row on the 24-well plates. Incubate at 37 degree C for 6 hours.

[1021] While cells are incubating, prepare appropriate media, either 1%BSA in DMEM with 1x penstrep, or HGS CHO-5 media (116.6 mg/L of CaCl2 (anhyd); 0.00130 mg/L $CuSO_4$-$5H_2O$; 0.050 mg/L of $Fe(NO_3)_3$-$9H_2O$; 0.417 mg/L of $FeSO_4$-$7H_2O$; 311.80 mg/L of Kcl; 28.64 mg/L of $MgCl_2$; 48.84 mg/L of $MgSO_4$; 6995.50 mg/L of NaCl; 2400.0 mg/L of $NaHCO_3$; 62.50 mg/L of NaH_2PO_4-H_20; 71.02 mg/L of Na_2HPO4; .4320 mg/L of $ZnSO_4$-$7H_2O$; .002 mg/L of Arachidonic Acid ; 1.022 mg/L of Cholesterol; .070 mg/L of DL-alpha-Tocopherol-Acetate; 0.0520 mg/L of Linoleic Acid; 0.010 mg/L of Linolenic Acid; 0.010 mg/L of Myristic Acid; 0.010 mg/L of Oleic Acid; 0.010 mg/L of Palmitric Acid; 0.010 mg/L of Palmitic Acid; 100 mg/L of Pluronic F-68; 0.010 mg/L of Stearic Acid; 2.20 mg/L of Tween 80; 4551 mg/L of D-Glucose; 130.85 mg/ml of L- Alanine; 147.50 mg/ml of L-Arginine-HCL; 7.50 mg/ml of L-Asparagine-H_20; 6.65 mg/ml of L-Aspartic Acid; 29.56 mg/ml of L-Cystine-2HCL-H_20; 31.29 mg/ml of L-Cystine-2HCL; 7.35 mg/ml of L-Glutamic Acid; 365.0 mg/ml of L-Glutamine; 18.75 mg/ml of Glycine; 52.48 mg/ml of L-Histidine-HCL-H_20; 106.97 mg/ml of L-Isoleucine; 111.45 mg/ml of L-Leucine; 163.75 mg/ml of L-Lysine HCL; 32.34 mg/ml of L-Methionine; 68.48 mg/ml of L-Phenylalainine; 40.0 mg/ml of L-Proline; 26.25 mg/ml of L-Serine; 101.05 mg/ml of L-Threonine; 19.22 mg/ml of L-Tryptophan; 91.79 mg/ml of L-Tryrosine-2Na-$2H_20$; and 99.65 mg/ml of L-Valine; 0.0035 mg/L of Biotin; 3.24 mg/L of D-Ca Pantothenate; 11.78 mg/L of Choline Chloride; 4.65 mg/L of Folic Acid; 15.60 mg/L of i-Inositol; 3.02 mg/L of Niacinamide; 3.00 mg/L of Pyridoxal HCL; 0.031 mg/L of Pyridoxine HCL; 0.319 mg/L of Riboflavin; 3.17 mg/L of Thiamine HCL; 0.365 mg/L of Thymidine; 0.680 mg/L of Vitamin B_{12}; 25 mM of HEPES Buffer; 2.39 mg/L of Na Hypoxanthine; 0.105 mg/L of Lipoic Acid; 0.081 mg/L of Sodium Putrescine-2HCL; 55.0 mg/L of Sodium Pyruvate; 0.0067 mg/L of Sodium Selenite; 20uM of Ethanolamine; 0.122 mg/L of Ferric Citrate; 41.70 mg/L of Methyl-B-Cyclodextrin complexed with Linoleic Acid; 33.33 mg/L of Methyl-B-Cyclodextrin complexed with Oleic Acid; 10 mg/L of Methyl-B-Cyclodextrin complexed with Retinal Acetate. Adjust osmolarity to 327 mOsm) with 2mm glutamine and 1x penstrep. (BSA (81-068-3 Bayer) 100gm dissolved in 1L DMEM for a 10% BSA stock solution). Filter the media and collect 50 ul for endotoxin assay in 15ml polystyrene conical.

[1022] The transfection reaction is terminated, preferably by tag-teaming, at the

end of the incubation period. Person A aspirates off the transfection media, while person B adds 1.5ml appropriate media to each well. Incubate at 37 degree C for 45 or 72 hours depending on the media used: 1%BSA for 45 hours or CHO-5 for 72 hours.

[1023] On day four, using a 300ul multichannel pipetter, aliquot 600ul in one 1ml deep well plate and the remaining supernatant into a 2ml deep well. The supernatants from each well can then be used in the assays described in Examples 32-39.

[1024] It is specifically understood that when activity is obtained in any of the assays described below using a supernatant, the activity originates from either the polypeptide of the present invention directly (e.g., as a secreted protein) or by polypeptide of the present invention inducing expression of other proteins, which are then secreted into the supernatant. Thus, the invention further provides a method of identifying the protein in the supernatant characterized by an activity in a particular assay.

Example 31: Construction of GAS Reporter Construct

[1025] One signal transduction pathway involved in the differentiation and proliferation of cells is called the Jaks-STATs pathway. Activated proteins in the Jaks-STATs pathway bind to gamma activation site "GAS" elements or interferon-sensitive responsive element ("ISRE"), located in the promoter of many genes. The binding of a protein to these elements alter the expression of the associated gene.

[1026] GAS and ISRE elements are recognized by a class of transcription factors called Signal Transducers and Activators of Transcription, or "STATs." There are six members of the STATs family. Stat1 and Stat3 are present in many cell types, as is Stat2 (as response to IFN-alpha is widespread). Stat4 is more restricted and is not in many cell types though it has been found in T helper class I, cells after treatment with IL-12. Stat5 was originally called mammary growth factor, but has been found at higher concentrations in other cells including myeloid cells. It can be activated in tissue culture cells by many cytokines.

[1027] The STATs are activated to translocate from the cytoplasm to the nucleus upon tyrosine phosphorylation by a set of kinases known as the Janus Kinase ("Jaks") family. Jaks represent a distinct family of soluble tyrosine kinases and include Tyk2, Jak1, Jak2, and Jak3. These kinases display significant sequence similarity and are

generally catalytically inactive in resting cells.

[1028] The Jaks are activated by a wide range of receptors summarized in the Table below. (Adapted from review by Schidler and Darnell, Ann. Rev. Biochem. 64:621-51 (1995).) A cytokine receptor family, capable of activating Jaks, is divided into two groups: (a) Class 1 includes receptors for IL-2, IL-3, IL-4, IL-6, IL-7, IL-9, IL-11, IL-12, IL-15, Epo, PRL, GH, G-CSF, GM-CSF, LIF, CNTF, and thrombopoietin; and (b) Class 2 includes IFN-a, IFN-g, and IL-10. The Class 1 receptors share a conserved cysteine motif (a set of four conserved cysteines and one tryptophan) and a WSXWS motif (a membrane proximal region encoding Trp-Ser-Xxx-Trp-Ser (SEQ ID NO:1882)).

[1029] Thus, on binding of a ligand to a receptor, Jaks are activated, which in turn activate STATs, which then translocate and bind to GAS elements. This entire process is encompassed in the Jaks-STATs signal transduction pathway.

[1030] Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the GAS or the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. For example, growth factors and cytokines are known to activate the Jaks-STATs pathway. (See Table below.) Thus, by using GAS elements linked to reporter molecules, activators of the Jaks-STATs pathway can be identified.

Ligand	tyk2	JAKs Jak1	Jak2	Jak3	STATS	GAS(elements) or ISRE
IFN family						
IFN-a/B	+	+	-	-	1,2,3	ISRE
IFN-g		+	+	-	1	GAS (IRF1>Lys6>IFP)
Il-10	+	?	?	-	1,3	
gp130 family						
IL-6 (Pleiotrohic)	+	+	+	?	1,3	GAS (IRF1>Lys6>IFP)
Il-11(Pleiotrohic)	?	+	?	?	1,3	
OnM(Pleiotrohic)	?	+	+	?	1,3	
LIF(Pleiotrohic)	?	+	+	?	1,3	
CNTF(Pleiotrohic)	-/+	+	+	?	1,3	
G-CSF(Pleiotrohic)	?	+	?	?	1,3	
IL-12(Pleiotrohic)	+	-	+	+	1,3	
g-C family						
IL-2 (lymphocytes)	-	+	-	+	1,3,5	GAS
IL-4 (lymph/myeloid)	-	+	-	+	6	GAS (IRF1 = IFP >>Ly6)(IgH)
IL-7 (lymphocytes)	-	+	-	+	5	GAS
IL-9 (lymphocytes)	-	+	-	+	5	GAS
IL-13 (lymphocyte)	-	+	?	?	6	GAS
IL-15	?	+	?	+	5	GAS
gp140 family						
IL-3 (myeloid)	-	-	+	-	5	GAS (IRF1>IFP>>Ly6)
IL-5 (myeloid)	-	-	+	-	5	GAS
GM-CSF (myeloid)	-	-	+	-	5	GAS
Growth hormone family						
GH	?	-	+	-	5	
PRL	?	+/-	+	-	1,3,5	
EPO	?	-	+	-	5	GAS(B-CAS>IRF1=IFP>>Ly6)
Receptor Tyrosine Kinases						
EGF	?	+	+	-	1,3	GAS (IRF1)
PDGF	?	+	+	-	1,3	
CSF-1	?	+	+	-	1,3	GAS (not IRF1)

[1031] To construct a synthetic GAS containing promoter element, which is used in the Biological Assays described in Examples 32-33, a PCR based strategy is employed to generate a GAS-SV40 promoter sequence. The 5' primer contains four tandem copies of the GAS binding site found in the IRF1 promoter and previously demonstrated to bind STATs upon induction with a range of cytokines (Rothman et al., Immunity 1:457-468 (1994).), although other GAS or ISRE elements can be used instead. The 5' primer also contains 18bp of sequence complementary to the SV40 early promoter sequence and is flanked with an XhoI site. The sequence of the 5' primer is:

5':GCGCCTCGAGATTTCCCCGAAATCTAGATTTCCCCGAAATGATTTCCCCGAA
ATGATTTCCCCGAAATATCTGCCATCTCAATTAG:3' (SEQ ID NO:1883).

[1032] The downstream primer is complementary to the SV40 promoter and is flanked with a Hind III site: 5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:1884).

[1033] PCR amplification is performed using the SV40 promoter template present in the B-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI/Hind III and subcloned into BLSK2-. (Stratagene.) Sequencing with forward and reverse primers confirms that the insert contains the following sequence:

5':CTCGAGATTTCCCCGAAATCTAGATTTCCCCGAAATGATTTCCCCGAAATGA
TTTCCCCGAAATATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTA
ACTCCGCCCATCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCGCCCCAT
GGCTGACTAATTTTTTTTATTTATGCAGAGGCCGAGGCCGCCTCGGCCTCTGAG
CTATTCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTTTGCAAAAA
GCTT:3' (SEQ ID NO:1885).

[1034] With this GAS promoter element linked to the SV40 promoter, a GAS:SEAP2 reporter construct is next engineered. Here, the reporter molecule is a secreted alkaline phosphatase, or "SEAP." Clearly, however, any reporter molecule can be instead of SEAP, in this or in any of the other Examples. Well known reporter molecules that can be used instead of SEAP include chloramphenicol acetyltransferase (CAT), luciferase, alkaline phosphatase, B-galactosidase, green fluorescent protein (GFP), or any protein detectable by an antibody.

[1035] The above sequence confirmed synthetic GAS-SV40 promoter element is subcloned into the pSEAP-Promoter vector obtained from Clontech using HindIII and

XhoI, effectively replacing the SV40 promoter with the amplified GAS:SV40 promoter element, to create the GAS-SEAP vector. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

[1036] Thus, in order to generate mammalian stable cell lines expressing the GAS-SEAP reporter, the GAS-SEAP cassette is removed from the GAS-SEAP vector using SalI and NotI, and inserted into a backbone vector containing the neomycin resistance gene, such as pGFP-1 (Clontech), using these restriction sites in the multiple cloning site, to create the GAS-SEAP/Neo vector. Once this vector is transfected into mammalian cells, this vector can then be used as a reporter molecule for GAS binding as described in Examples 32-33.

[1037] Other constructs can be made using the above description and replacing GAS with a different promoter sequence. For example, construction of reporter molecules containing NFK-B and EGR promoter sequences are described in Examples 34 and 35. However, many other promoters can be substituted using the protocols described in these Examples. For instance, SRE, IL-2, NFAT, or Osteocalcin promoters can be substituted, alone or in combination (e.g., GAS/NF-KB/EGR, GAS/NF-KB, Il-2/NFAT, or NF-KB/GAS). Similarly, other cell lines can be used to test reporter construct activity, such as HELA (epithelial), HUVEC (endothelial), Reh (B-cell), Saos-2 (osteoblast), HUVAC (aortic), or Cardiomyocyte.

Example 32: High-Throughput Screening Assay for T-cell Activity.

[1038] The following protocol is used to assess T-cell activity by identifying factors, and determining whether supernate containing a polypeptide of the invention proliferates and/or differentiates T-cells. T-cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 31. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The T-cell used in this assay is Jurkat T-cells (ATCC Accession No. TIB-152), although Molt-3 cells (ATCC Accession No. CRL-1552) and Molt-4 cells (ATCC Accession No. CRL-1582) cells can also be used.

[1039] Jurkat T-cells are lymphoblastic CD4+ Th1 helper cells. In order to

generate stable cell lines, approximately 2 million Jurkat cells are transfected with the GAS-SEAP/neo vector using DMRIE-C (Life Technologies)(transfection procedure described below). The transfected cells are seeded to a density of approximately 20,000 cells per well and transfectants resistant to 1 mg/ml genticin selected. Resistant colonies are expanded and then tested for their response to increasing concentrations of interferon gamma. The dose response of a selected clone is demonstrated.

[1040] Specifically, the following protocol will yield sufficient cells for 75 wells containing 200 ul of cells. Thus, it is either scaled up, or performed in multiple to generate sufficient cells for multiple 96 well plates. Jurkat cells are maintained in RPMI + 10% serum with 1%Pen-Strep. Combine 2.5 mls of OPTI-MEM (Life Technologies) with 10 ug of plasmid DNA in a T25 flask. Add 2.5 ml OPTI-MEM containing 50 ul of DMRIE-C and incubate at room temperature for 15-45 mins.

[1041] During the incubation period, count cell concentration, spin down the required number of cells (10^7 per transfection), and resuspend in OPTI-MEM to a final concentration of 10^7 cells/ml. Then add 1ml of 1 x 10^7 cells in OPTI-MEM to T25 flask and incubate at 37 degree C for 6 hrs. After the incubation, add 10 ml of RPMI + 15% serum.

[1042] The Jurkat:GAS-SEAP stable reporter lines are maintained in RPMI + 10% serum, 1 mg/ml Genticin, and 1% Pen-Strep. These cells are treated with supernatants containing polypeptide of the present invention or polypeptide of the present invention induced polypeptides as produced by the protocol described in Example 30.

[1043] On the day of treatment with the supernatant, the cells should be washed and resuspended in fresh RPMI + 10% serum to a density of 500,000 cells per ml. The exact number of cells required will depend on the number of supernatants being screened. For one 96 well plate, approximately 10 million cells (for 10 plates, 100 million cells) are required.

[1044] Transfer the cells to a triangular reservoir boat, in order to dispense the cells into a 96 well dish, using a 12 channel pipette. Using a 12 channel pipette, transfer 200 ul of cells into each well (therefore adding 100, 000 cells per well).

[1045] After all the plates have been seeded, 50 ul of the supernatants are transferred directly from the 96 well plate containing the supernatants into each well using a 12 channel pipette. In addition, a dose of exogenous interferon gamma (0.1, 1.0, 10 ng)

is added to wells H9, H10, and H11 to serve as additional positive controls for the assay.

[1046] The 96 well dishes containing Jurkat cells treated with supernatants are placed in an incubator for 48 hrs (note: this time is variable between 48-72 hrs). 35 ul samples from each well are then transferred to an opaque 96 well plate using a 12 channel pipette. The opaque plates should be covered (using sellophene covers) and stored at -20 degree C until SEAP assays are performed according to Example 36. The plates containing the remaining treated cells are placed at 4 degree C and serve as a source of material for repeating the assay on a specific well if desired.

[1047] As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate Jurkat T cells. Over 30 fold induction is typically observed in the positive control wells.

[1048] The above protocol may be used in the generation of both transient, as well as, stable transfected cells, which would be apparent to those of skill in the art.

Example 33: High-Throughput Screening Assay Identifying Myeloid Activity

[1049] The following protocol is used to assess myeloid activity of polypeptide of the present invention by determining whether polypeptide of the present invention proliferates and/or differentiates myeloid cells. Myeloid cell activity is assessed using the GAS/SEAP/Neo construct produced in Example 31. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The myeloid cell used in this assay is U937, a pre-monocyte cell line, although TF-1, HL60, or KG1 can be used.

[1050] To transiently transfect U937 cells with the GAS/SEAP/Neo construct produced in Example 31, a DEAE-Dextran method (Kharbanda et. al., 1994, Cell Growth & Differentiation, 5:259-265) is used. First, harvest $2x10e^7$ U937 cells and wash with PBS. The U937 cells are usually grown in RPMI 1640 medium containing 10% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 mg/ml streptomycin.

[1051] Next, suspend the cells in 1 ml of 20 mM Tris-HCl (pH 7.4) buffer containing 0.5 mg/ml DEAE-Dextran, 8 ug GAS-SEAP2 plasmid DNA, 140 mM NaCl, 5 mM KCl, 375 uM $Na_2HPO_4.7H_2O$, 1 mM $MgCl_2$, and 675 uM $CaCl_2$. Incubate at 37

degrees C for 45 min.

[1052] Wash the cells with RPMI 1640 medium containing 10% FBS and then resuspend in 10 ml complete medium and incubate at 37 degree C for 36 hr.

The GAS-SEAP/U937 stable cells are obtained by growing the cells in 400 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 400 ug/ml G418 for couple of passages.

[1053] These cells are tested by harvesting $1x10^8$ cells (this is enough for ten 96-well plates assay) and wash with PBS. Suspend the cells in 200 ml above described growth medium, with a final density of $5x10^5$ cells/ml. Plate 200 ul cells per well in the 96-well plate (or $1x10^5$ cells/well).

[1054] Add 50 ul of the supernatant prepared by the protocol described in Example 30. Incubate at 37 degee C for 48 to 72 hr. As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate U937 cells. Over 30 fold induction is typically observed in the positive control wells. SEAP assay the supernatant according to the protocol described in Example 36.

Example 34: High-Throughput Screening Assay Identifying Neuronal Activity.

[1055] When cells undergo differentiation and proliferation, a group of genes are activated through many different signal transduction pathways. One of these genes, EGR1 (early growth response gene 1), is induced in various tissues and cell types upon activation. The promoter of EGR1 is responsible for such induction. Using the EGR1 promoter linked to reporter molecules, activation of cells can be assessed by polypeptide of the present invention.

[1056] Particularly, the following protocol is used to assess neuronal activity in PC12 cell lines. PC12 cells (rat phenochromocytoma cells) are known to proliferate and/or differentiate by activation with a number of mitogens, such as TPA (tetradecanoyl phorbol acetate), NGF (nerve growth factor), and EGF (epidermal growth factor). The EGR1 gene expression is activated during this treatment. Thus, by stably transfecting PC12 cells with a construct containing an EGR promoter linked to SEAP reporter, activation of PC12 cells by polypeptide of the present invention can be assessed.

[1057] The EGR/SEAP reporter construct can be assembled by the following

protocol. The EGR-1 promoter sequence (-633 to +1)(Sakamoto K et al., Oncogene 6:867-871 (1991)) can be PCR amplified from human genomic DNA using the following primers:

5' GCGCTCGAGGGATGACAGCGATAGAACCCCGG -3' (SEQ ID NO: 1886)

and

5' GCGAAGCTTCGCGACTCCCCGGATCCGCCTC-3' (SEQ ID NO: 1887).

[1058] Using the GAS:SEAP/Neo vector produced in Example 31, EGR1 amplified product can then be inserted into this vector. Linearize the GAS:SEAP/Neo vector using restriction enzymes XhoI/HindIII, removing the GAS/SV40 stuffer. Restrict the EGR1 amplified product with these same enzymes. Ligate the vector and the EGR1 promoter.

[1059] To prepare 96 well-plates for cell culture, two mls of a coating solution (1:30 dilution of collagen type I (Upstate Biotech Inc. Cat#08-115) in 30% ethanol (filter sterilized)) is added per one 10 cm plate or 50 ml per well of the 96-well plate, and allowed to air dry for 2 hr.

[1060] PC12 cells are routinely grown in RPMI-1640 medium (Bio Whittaker) containing 10% horse serum (JRH BIOSCIENCES, Cat. # 12449-78P), 5% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 ug/ml streptomycin on a precoated 10 cm tissue culture dish. One to four split is done every three to four days. Cells are removed from the plates by scraping and resuspended with pipetting up and down for more than 15 times.

[1061] Transfect the EGR/SEAP/Neo construct into PC12 using the Lipofectamine protocol described in Example 30. EGR-SEAP/PC12 stable cells are obtained by growing the cells in 300 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 300 ug/ml G418 for couple of passages.

[1062] To assay for neuronal activity, a 10 cm plate with cells around 70 to 80% confluent is screened by removing the old medium. Wash the cells once with PBS (Phosphate buffered saline). Then starve the cells in low serum medium (RPMI-1640 containing 1% horse serum and 0.5% FBS with antibiotics) overnight.

[1063] The next morning, remove the medium and wash the cells with PBS. Scrape off the cells from the plate, suspend the cells well in 2 ml low serum medium.

Count the cell number and add more low serum medium to reach final cell density as $5x10^5$ cells/ml.

[1064] Add 200 ul of the cell suspension to each well of 96-well plate (equivalent to $1x10^5$ cells/well). Add 50 ul supernatant produced by Example 30, 37 degree C for 48 to 72 hr. As a positive control, a growth factor known to activate PC12 cells through EGR can be used, such as 50 ng/ul of Neuronal Growth Factor (NGF). Over fifty-fold induction of SEAP is typically seen in the positive control wells. SEAP assay the supernatant according to Example 36.

Example 35: High-Throughput Screening Assay for T-cell Activity

[1065] NF-KB (Nuclear Factor KB) is a transcription factor activated by a wide variety of agents including the inflammatory cytokines IL-1 and TNF, CD30 and CD40, lymphotoxin-alpha and lymphotoxin-beta, by exposure to LPS or thrombin, and by expression of certain viral gene products. As a transcription factor, NF-KB regulates the expression of genes involved in immune cell activation, control of apoptosis (NF- KB appears to shield cells from apoptosis), B and T-cell development, anti-viral and antimicrobial responses, and multiple stress responses.

[1066] In non-stimulated conditions, NF- KB is retained in the cytoplasm with I-KB (Inhibitor KB). However, upon stimulation, I- KB is phosphorylated and degraded, causing NF- KB to shuttle to the nucleus, thereby activating transcription of target genes. Target genes activated by NF- KB include IL-2, IL-6, GM-CSF, ICAM-1 and class 1 MHC.

[1067] Due to its central role and ability to respond to a range of stimuli, reporter constructs utilizing the NF-KB promoter element are used to screen the supernatants produced in Example 30. Activators or inhibitors of NF-KB would be useful in treating, preventing, and/or diagnosing diseases. For example, inhibitors of NF-KB could be used to treat those diseases related to the acute or chronic activation of NF-KB, such as rheumatoid arthritis.

[1068] To construct a vector containing the NF-KB promoter element, a PCR based strategy is employed. The upstream primer contains four tandem copies of the NF-KB binding site (GGGGACTTTCCC) (SEQ ID NO:1888), 18 bp of sequence

complementary to the 5' end of the SV40 early promoter sequence, and is flanked with an XhoI site:

5':GCGGCCTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGACTTT CCATCCTGCCATCTCAATTAG:3' (SEQ ID NO:1889).

[1069] The downstream primer is complementary to the 3' end of the SV40 promoter and is flanked with a Hind III site:

5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:1884).

[1070] PCR amplification is performed using the SV40 promoter template present in the pB-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI and Hind III and subcloned into BLSK2-. (Stratagene) Sequencing with the T7 and T3 primers confirms the insert contains the following sequence:

5':CTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGACTTTCCATC TGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACTCCGCCCATCCC GCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCGCCCCATGGCTGACTAATTTT TTTTATTTATGCAGAGGCCGAGGCCGCCTCGGCCTCTGAGCTATTCCAGAAGT AGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTTTGCAAAAAGCTT:3' (SEQ ID NO:1890).

[1071] Next, replace the SV40 minimal promoter element present in the pSEAP2-promoter plasmid (Clontech) with this NF-KB/SV40 fragment using XhoI and HindIII. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

[1072] In order to generate stable mammalian cell lines, the NF-KB/SV40/SEAP cassette is removed from the above NF-KB/SEAP vector using restriction enzymes SalI and NotI, and inserted into a vector containing neomycin resistance. Particularly, the NF-KB/SV40/SEAP cassette was inserted into pGFP-1 (Clontech), replacing the GFP gene, after restricting pGFP-1 with SalI and NotI.

[1073] Once NF-KB/SV40/SEAP/Neo vector is created, stable Jurkat T-cells are created and maintained according to the protocol described in Example 32. Similarly, the method for assaying supernatants with these stable Jurkat T-cells is also described in Example 32. As a positive control, exogenous TNF alpha (0.1,1, 10 ng) is added to wells H9, H10, and H11, with a 5-10 fold activation typically observed.

Example 36: Assay for SEAP Activity

[1074] As a reporter molecule for the assays described in Examples 32-35, SEAP activity is assayed using the Tropix Phospho-light Kit (Cat. BP-400) according to the following general procedure. The Tropix Phospho-light Kit supplies the Dilution, Assay, and Reaction Buffers used below.

[1075] Prime a dispenser with the 2.5x Dilution Buffer and dispense 15 ul of 2.5x dilution buffer into Optiplates containing 35 ul of a supernatant. Seal the plates with a plastic sealer and incubate at 65 degree C for 30 min. Separate the Optiplates to avoid uneven heating.

[1076] Cool the samples to room temperature for 15 minutes. Empty the dispenser and prime with the Assay Buffer. Add 50 ml Assay Buffer and incubate at room temperature 5 min. Empty the dispenser and prime with the Reaction Buffer (see the table below). Add 50 ul Reaction Buffer and incubate at room temperature for 20 minutes. Since the intensity of the chemiluminescent signal is time dependent, and it takes about 10 minutes to read 5 plates on luminometer, one should treat 5 plates at each time and start the second set 10 minutes later.

[1077] Read the relative light unit in the luminometer. Set H12 as blank, and print the results. An increase in chemiluminescence indicates reporter activity.

Reaction Buffer Formulation:

# of plates	Rxn buffer diluent (ml)	CSPD (ml)
10	60	3
11	65	3.25
12	70	3.5
13	75	3.75
14	80	4
15	85	4.25
16	90	4.5
17	95	4.75
18	100	5
19	105	5.25

20	110	5.5
21	115	5.75
22	120	6
23	125	6.25
24	130	6.5
25	135	6.75
26	140	7
27	145	7.25
28	150	7.5
29	155	7.75
30	160	8
31	165	8.25
32	170	8.5
33	175	8.75
34	180	9
35	185	9.25
36	190	9.5
37	195	9.75
38	200	10
39	205	10.25
40	210	10.5
41	215	10.75
42	220	11
43	225	11.25
44	230	11.5
45	235	11.75
46	240	12
47	245	12.25
48	250	12.5
49	255	12.75
50	260	13

Example 37: High-Throughput Screening Assay Identifying Changes in Small Molecule Concentration and Membrane Permeability

[1078] Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium, sodium, and pH, as well as alter membrane

potential. These alterations can be measured in an assay to identify supernatants which bind to receptors of a particular cell. Although the following protocol describes an assay for calcium, this protocol can easily be modified to detect changes in potassium, sodium, pH, membrane potential, or any other small molecule which is detectable by a fluorescent probe.

[1079] The following assay uses Fluorometric Imaging Plate Reader ("FLIPR") to measure changes in fluorescent molecules (Molecular Probes) that bind small molecules. Clearly, any fluorescent molecule detecting a small molecule can be used instead of the calcium fluorescent molecule, fluo-4 (Molecular Probes, Inc.; catalog no. F-14202), used here.

[1080] For adherent cells, seed the cells at 10,000 -20,000 cells/well in a Co-star black 96-well plate with clear bottom. The plate is incubated in a CO_2 incubator for 20 hours. The adherent cells are washed two times in Biotek washer with 200 ul of HBSS (Hank's Balanced Salt Solution) leaving 100 ul of buffer after the final wash.

[1081] A stock solution of 1 mg/ml fluo-4 is made in 10% pluronic acid DMSO. To load the cells with fluo-4 , 50 ul of 12 ug/ml fluo-4 is added to each well. The plate is incubated at 37 degrees C in a CO_2 incubator for 60 min. The plate is washed four times in the Biotek washer with HBSS leaving 100 ul of buffer.

[1082] For non-adherent cells, the cells are spun down from culture media. Cells are re-suspended to 2-5x10^6 cells/ml with HBSS in a 50-ml conical tube. 4 ul of 1 mg/ml fluo-4 solution in 10% pluronic acid DMSO is added to each ml of cell suspension. The tube is then placed in a 37 degrees C water bath for 30-60 min. The cells are washed twice with HBSS, resuspended to 1x10^6 cells/ml, and dispensed into a microplate, 100 ul/well. The plate is centrifuged at 1000 rpm for 5 min. The plate is then washed once in Denley Cell Wash with 200 ul, followed by an aspiration step to 100 ul final volume.

[1083] For a non-cell based assay, each well contains a fluorescent molecule, such as fluo-4 . The supernatant is added to the well, and a change in fluorescence is detected.

[1084] To measure the fluorescence of intracellular calcium, the FLIPR is set for the following parameters: (1) System gain is 300-800 mW; (2) Exposure time is 0.4 second; (3) Camera F/stop is F/2; (4) Excitation is 488 nm; (5) Emission is 530 nm; and (6) Sample addition is 50 ul. Increased emission at 530 nm indicates an extracellular signaling event caused by the a molecule, either polypeptide of the present invention or a

molecule induced by polypeptide of the present invention, which has resulted in an increase in the intracellular Ca^{++} concentration.

Example 38: High-Throughput Screening Assay Identifying Tyrosine Kinase Activity

[1085] The Protein Tyrosine Kinases (PTK) represent a diverse group of transmembrane and cytoplasmic kinases. Within the Receptor Protein Tyrosine Kinase RPTK) group are receptors for a range of mitogenic and metabolic growth factors including the PDGF, FGF, EGF, NGF, HGF and Insulin receptor subfamilies. In addition there are a large family of RPTKs for which the corresponding ligand is unknown. Ligands for RPTKs include mainly secreted small proteins, but also membrane-bound and extracellular matrix proteins.

[1086] Activation of RPTK by ligands involves ligand-mediated receptor dimerization, resulting in transphosphorylation of the receptor subunits and activation of the cytoplasmic tyrosine kinases. The cytoplasmic tyrosine kinases include receptor associated tyrosine kinases of the src-family (e.g., src, yes, lck, lyn, fyn) and non-receptor linked and cytosolic protein tyrosine kinases, such as the Jak family, members of which mediate signal transduction triggered by the cytokine superfamily of receptors (e.g., the Interleukins, Interferons, GM-CSF, and Leptin).

[1087] Because of the wide range of known factors capable of stimulating tyrosine kinase activity, identifying whether polypeptide of the present invention or a molecule induced by polypeptide of the present invention is capable of activating tyrosine kinase signal transduction pathways is of interest. Therefore, the following protocol is designed to identify such molecules capable of activating the tyrosine kinase signal transduction pathways.

[1088] Seed target cells (e.g., primary keratinocytes) at a density of approximately 25,000 cells per well in a 96 well Loprodyne Silent Screen Plates purchased from Nalge Nunc (Naperville, IL). The plates are sterilized with two 30 minute rinses with 100% ethanol, rinsed with water and dried overnight. Some plates are coated for 2 hr with 100 ml of cell culture grade type I collagen (50 mg/ml), gelatin (2%) or polylysine (50 mg/ml), all of which can be purchased from Sigma Chemicals (St. Louis, MO) or 10% Matrigel purchased from Becton Dickinson (Bedford,MA), or calf serum, rinsed with

PBS and stored at 4 degree C. Cell growth on these plates is assayed by seeding 5,000 cells/well in growth medium and indirect quantitation of cell number through use of alamarBlue as described by the manufacturer Alamar Biosciences, Inc. (Sacramento, CA) after 48 hr. Falcon plate covers #3071 from Becton Dickinson (Bedford,MA) are used to cover the Loprodyne Silent Screen Plates. Falcon Microtest III cell culture plates can also be used in some proliferation experiments.

[1089] To prepare extracts, A431 cells are seeded onto the nylon membranes of Loprodyne plates (20,000/200ml/well) and cultured overnight in complete medium. Cells are quiesced by incubation in serum-free basal medium for 24 hr. After 5-20 minutes treatment with EGF (60ng/ml) or 50 ul of the supernatant produced in Example 30, the medium was removed and 100 ml of extraction buffer ((20 mM HEPES pH 7.5, 0.15 M NaCl, 1% Triton X-100, 0.1% SDS, 2 mM Na3VO4, 2 mM Na4P2O7 and a cocktail of protease inhibitors (# 1836170) obtained from Boeheringer Mannheim (Indianapolis, IN) is added to each well and the plate is shaken on a rotating shaker for 5 minutes at 4^oC. The plate is then placed in a vacuum transfer manifold and the extract filtered through the 0.45 mm membrane bottoms of each well using house vacuum. Extracts are collected in a 96-well catch/assay plate in the bottom of the vacuum manifold and immediately placed on ice. To obtain extracts clarified by centrifugation, the content of each well, after detergent solubilization for 5 minutes, is removed and centrifuged for 15 minutes at 4 degree C at 16,000 x g.

[1090] Test the filtered extracts for levels of tyrosine kinase activity. Although many methods of detecting tyrosine kinase activity are known, one method is described here.

[1091] Generally, the tyrosine kinase activity of a supernatant is evaluated by determining its ability to phosphorylate a tyrosine residue on a specific substrate (a biotinylated peptide). Biotinylated peptides that can be used for this purpose include PSK1 (corresponding to amino acids 6-20 of the cell division kinase cdc2-p34) and PSK2 (corresponding to amino acids 1-17 of gastrin). Both peptides are substrates for a range of tyrosine kinases and are available from Boehringer Mannheim.

[1092] The tyrosine kinase reaction is set up by adding the following components in order. First, add 10ul of 5uM Biotinylated Peptide, then 10ul ATP/Mg_{2+} (5mM

ATP/50mM $MgCl_2$), then 10ul of 5x Assay Buffer (40mM imidazole hydrochloride, pH7.3, 40 mM beta-glycerophosphate, 1mM EGTA, 100mM $MgCl_2$, 5 mM $MnCl_2$, 0.5 mg/ml BSA), then 5ul of Sodium Vanadate(1mM), and then 5ul of water. Mix the components gently and preincubate the reaction mix at 30 degree C for 2 min. Initial the reaction by adding 10ul of the control enzyme or the filtered supernatant.

[1093] The tyrosine kinase assay reaction is then terminated by adding 10 ul of 120mm EDTA and place the reactions on ice.

[1094] Tyrosine kinase activity is determined by transferring 50 ul aliquot of reaction mixture to a microtiter plate (MTP) module and incubating at 37 degree C for 20 min. This allows the streptavadin coated 96 well plate to associate with the biotinylated peptide. Wash the MTP module with 300ul/well of PBS four times. Next add 75 ul of anti-phospotyrosine antibody conjugated to horse radish peroxidase(anti-P-Tyr-POD(0.5u/ml)) to each well and incubate at 37 degree C for one hour. Wash the well as above.

[1095] Next add 100ul of peroxidase substrate solution (Boehringer Mannheim) and incubate at room temperature for at least 5 mins (up to 30 min). Measure the absorbance of the sample at 405 nm by using ELISA reader. The level of bound peroxidase activity is quantitated using an ELISA reader and reflects the level of tyrosine kinase activity.

Example 39: High-Throughput Screening Assay Identifying Phosphorylation Activity

[1096] As a potential alternative and/or compliment to the assay of protein tyrosine kinase activity described in Example 38, an assay which detects activation (phosphorylation) of major intracellular signal transduction intermediates can also be used. For example, as described below one particular assay can detect tyrosine phosphorylation of the Erk-1 and Erk-2 kinases. However, phosphorylation of other molecules, such as Raf, JNK, p38 MAP, Map kinase kinase (MEK), MEK kinase, Src, Muscle specific kinase (MuSK), IRAK, Tec, and Janus, as well as any other phosphoserine, phosphotyrosine, or phosphothreonine molecule, can be detected by substituting these molecules for Erk-1 or Erk-2 in the following assay.

[1097] Specifically, assay plates are made by coating the wells of a 96-well ELISA

plate with 0.1ml of protein G (1ug/ml) for 2 hr at room temp, (RT). The plates are then rinsed with PBS and blocked with 3% BSA/PBS for 1 hr at RT. The protein G plates are then treated with 2 commercial monoclonal antibodies (100ng/well) against Erk-1 and Erk-2 (1 hr at RT) (Santa Cruz Biotechnology). (To detect other molecules, this step can easily be modified by substituting a monoclonal antibody detecting any of the above described molecules.) After 3-5 rinses with PBS, the plates are stored at 4 degree C until use.

[1098] A431 cells are seeded at 20,000/well in a 96-well Loprodyne filterplate and cultured overnight in growth medium. The cells are then starved for 48 hr in basal medium (DMEM) and then treated with EGF (6ng/well) or 50 ul of the supernatants obtained in Example 30 for 5-20 minutes. The cells are then solubilized and extracts filtered directly into the assay plate.

[1099] After incubation with the extract for 1 hr at RT, the wells are again rinsed. As a positive control, a commercial preparation of MAP kinase (10ng/well) is used in place of A431 extract. Plates are then treated with a commercial polyclonal (rabbit) antibody (1ug/ml) which specifically recognizes the phosphorylated epitope of the Erk-1 and Erk-2 kinases (1 hr at RT). This antibody is biotinylated by standard procedures. The bound polyclonal antibody is then quantitated by successive incubations with Europium-streptavidin and Europium fluorescence enhancing reagent in the Wallac DELFIA instrument (time-resolved fluorescence). An increased fluorescent signal over background indicates a phosphorylation by polypeptide of the present invention or a molecule induced by polypeptide of the present invention.

Example 40: Assay for the Stimulation of Bone Marrow CD34+ Cell Proliferation

[1100] This assay is based on the ability of human CD34+ to proliferate in the presence of hematopoietic growth factors and evaluates the ability of isolated polypeptides expressed in mammalian cells to stimulate proliferation of CD34+ cells.

[1101] It has been previously shown that most mature precursors will respond to only a single signal. More immature precursors require at least two signals to respond. Therefore, to test the effect of polypeptides on hematopoietic activity of a wide range of progenitor cells, the assay contains a given polypeptide in the presence or absence of other

hematopoietic growth factors. Isolated cells are cultured for 5 days in the presence of Stem Cell Factor (SCF) in combination with tested sample. SCF alone has a very limited effect on the proliferation of bone marrow (BM) cells, acting in such conditions only as a "survival" factor. However, combined with any factor exhibiting stimulatory effect on these cells (e.g., IL-3), SCF will cause a synergistic effect. Therefore, if the tested polypeptide has a stimulatory effect on a hematopoietic progenitors, such activity can be easily detected. Since normal BM cells have a low level of cycling cells, it is likely that any inhibitory effect of a given polypeptide, or agonists or antagonists thereof, might not be detected. Accordingly, assays for an inhibitory effect on progenitors is preferably tested in cells that are first subjected to *in vitro* stimulation with SCF+IL+3, and then contacted with the compound that is being evaluated for inhibition of such induced proliferation.

[1102] Briefly, CD34+ cells are isolated using methods known in the art. The cells are thawed and resuspended in medium (QBSF 60 serum-free medium with 1% L-glutamine (500ml) Quality Biological, Inc., Gaithersburg, MD Cat# 160-204-101). After several gentle centrifugation steps at 200 x g, cells are allowed to rest for one hour. The cell count is adjusted to 2.5 x 10^5 cells/ml. During this time, 100 μl of sterile water is added to the peripheral wells of a 96-well plate. The cytokines that can be tested with a given polypeptide in this assay is rhSCF (R&D Systems, Minneapolis, MN, Cat# 255-SC) at 50 ng/ml alone and in combination with rhSCF and rhIL-3 (R&D Systems, Minneapolis, MN, Cat# 203-ML) at 30 ng/ml. After one hour, 10 μl of prepared cytokines, 50 μl of the supernatants prepared in Example 30 (supernatants at 1:2 dilution = 50 μl) and 20 μl of diluted cells are added to the media which is already present in the wells to allow for a final total volume of 100 μl. The plates are then placed in a 37°C/5% CO_2 incubator for five days.

[1103] Eighteen hours before the assay is harvested, 0.5 μCi/well of [3H] Thymidine is added in a 10 μl volume to each well to determine the proliferation rate. The experiment is terminated by harvesting the cells from each 96-well plate to a filtermat using the Tomtec Harvester 96. After harvesting, the filtermats are dried, trimmed and placed into OmniFilter assemblies consisting of one OmniFilter plate and one OmniFilter Tray. 60 μl Microscint is added to each well and the plate sealed with TopSeal-A press-on

sealing film A bar code 15 sticker is affixed to the first plate for counting. The sealed plates is then loaded and the level of radioactivity determined via the Packard Top Count and the printed data collected for analysis. The level of radioactivity reflects the amount of cell proliferation.

[1104] The studies described in this example test the activity of a given polypeptide to stimulate bone marrow CD34+ cell proliferation. One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof. As a nonlimiting example, potential antagonists tested in this assay would be expected to inhibit cell proliferation in the presence of cytokines and/or to increase the inhibition of cell proliferation in the presence of cytokines and a given polypeptide. In contrast, potential agonists tested in this assay would be expected to enhance cell proliferation and/or to decrease the inhibition of cell proliferation in the presence of cytokines and a given polypeptide.

[1105] The ability of a gene to stimulate the proliferation of bone marrow CD34+ cells indicates that polynucleotides and polypeptides corresponding to the gene are useful for the diagnosis and treatment of disorders affecting the immune system and hematopoiesis. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections above, and elsewhere herein.

Example 41: Assay for Extracellular Matrix Enhanced Cell Response (EMECR)

[1106] The objective of the Extracellular Matrix Enhanced Cell Response (EMECR) assay is to identify gene products (e.g., isolated polypeptides) that act on the hematopoietic stem cells in the context of the extracellular matrix (ECM) induced signal.

[1107] Cells respond to the regulatory factors in the context of signal(s) received from the surrounding microenvironment. For example, fibroblasts, and endothelial and epithelial stem cells fail to replicate in the absence of signals from the ECM. Hematopoietic stem cells can undergo self-renewal in the bone marrow, but not in *in vitro* suspension culture. The ability of stem cells to undergo self-renewal *in vitro* is dependent upon their interaction with the stromal cells and the ECM protein fibronectin (fn). Adhesion of cells to fn is mediated by the $\alpha_5.\beta_1$ and $\alpha_4.\beta_1$ integrin receptors, which are

expressed by human and mouse hematopoietic stem cells. The factor(s) which integrate with the ECM environment and responsible for stimulating stem cell self-renewal has not yet been identified. Discovery of such factors should be of great interest in gene therapy and bone marrow transplant applications

[1108] Briefly, polystyrene, non tissue culture treated, 96-well plates are coated with fn fragment at a coating concentration of 0.2 μg/ cm^2. Mouse bone marrow cells are plated (1,000 cells/well) in 0.2 ml of serum-free medium. Cells cultured in the presence of IL-3 (5 ng/ml) + SCF (50 ng/ml) would serve as the positive control, conditions under which little self-renewal but pronounced differentiation of the stem cells is to be expected. Gene products of the invention (e.g., including, but not limited to, polynucleotides and polypeptides of the present invention, and supernatants produced in Example 30), are tested with appropriate negative controls in the presence and absence of SCF(5.0 ng/ml), where test factor supernates represent 10% of the total assay volume. The plated cells are then allowed to grow by incubating in a low oxygen environment (5% CO_2, 7% O_2, and 88% N_2) tissue culture incubator for 7 days. The number of proliferating cells within the wells is then quantitated by measuring thymidine incorporation into cellular DNA. Verification of the positive hits in the assay will require phenotypic characterization of the cells, which can be accomplished by scaling up of the culture system and using appropriate antibody reagents against cell surface antigens and FACScan.

[1109] One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

[1110] If a particular polypeptide of the present invention is found to be a stimulator of hematopoietic progenitors, polynucleotides and polypeptides corresponding to the gene encoding said polypeptide may be useful for the diagnosis and treatment of disorders affecting the immune system and hematopoiesis. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections above, and elsewhere herein. The gene product may also be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

[1111] Additionally, the polynucleotides and/or polypeptides of the gene of

interest and/or agonists and/or antagonists thereof, may also be employed to inhibit the proliferation and differentiation of hematopoietic cells and therefore may be employed to protect bone marrow stem cells from chemotherapeutic agents during chemotherapy. This antiproliferative effect may allow administration of higher doses of chemotherapeutic agents and, therefore, more effective chemotherapeutic treatment.

[1112] Moreover, polynucleotides and polypeptides corresponding to the gene of interest may also be useful for the treatment and diagnosis of hematopoietic related disorders such as, for example, anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia.

Example 42: Human Dermal Fibroblast and Aortic Smooth Muscle Cell Proliferation

[1113] The polypeptide of interest is added to cultures of normal human dermal fibroblasts (NHDF) and human aortic smooth muscle cells (AoSMC) and two co-assays are performed with each sample. The first assay examines the effect of the polypeptide of interest on the proliferation of normal human dermal fibroblasts (NHDF) or aortic smooth muscle cells (AoSMC). Aberrant growth of fibroblasts or smooth muscle cells is a part of several pathological processes, including fibrosis, and restenosis. The second assay examines IL6 production by both NHDF and SMC. IL6 production is an indication of functional activation. Activated cells will have increased production of a number of cytokines and other factors, which can result in a proinflammatory or immunomodulatory outcome. Assays are run with and without co-TNFa stimulation, in order to check for costimulatory or inhibitory activity.

[1114] Briefly, on day 1, 96-well black plates are set up with 1000 cells/well (NHDF) or 2000 cells/well (AoSMC) in 100 μl culture media. NHDF culture media contains: Clonetics FB basal media, 1mg/ml hFGF, 5mg/ml insulin, 50mg/ml gentamycin, 2%FBS, while AoSMC culture media contains Clonetics SM basal media, 0.5 μg/ml hEGF, 5mg/ml insulin, 1μg/ml hFGF, 50mg/ml gentamycin, 50 μg/ml Amphotericin B, 5%FBS. After incubation at 37°C for at least 4-5 hours, culture media is aspirated and replaced with growth arrest media. Growth arrest media for NHDF contains fibroblast

basal media, 50mg/ml gentamycin, 2% FBS, while growth arrest media for AoSMC contains SM basal media, 50mg/ml gentamycin, 50μg/ml Amphotericin B, 0.4% FBS. Incubate at 37°C until day 2.

[1115] On day 2, serial dilutions and templates of the polypeptide of interest are designed such that they always include media controls and known-protein controls. For both stimulation and inhibition experiments, proteins are diluted in growth arrest media. For inhibition experiments, TNFa is added to a final concentration of 2ng/ml (NHDF) or 5ng/ml (AoSMC). Add 1/3 vol media containing controls or polypeptides of the present invention and incubate at 37°C/5% CO_2 until day 5.

[1116] Transfer 60μl from each well to another labeled 96-well plate, cover with a plate-sealer, and store at 4°C until Day 6 (for IL6 ELISA). To the remaining 100 μl in the cell culture plate, aseptically add Alamar Blue in an amount equal to 10% of the culture volume (10μl). Return plates to incubator for 3 to 4 hours. Then measure fluorescence with excitation at 530nm and emission at 590nm using the CytoFluor. This yields the growth stimulation/inhibition data.

[1117] On day 5, the IL6 ELISA is performed by coating a 96 well plate with 50-100 ul/well of Anti-Human IL6 Monoclonal antibody diluted in PBS, pH 7.4, incubate ON at room temperature.

[1118] On day 6, empty the plates into the sink and blot on paper towels. Prepare Assay Buffer containing PBS with 4% BSA. Block the plates with 200 μl/well of Pierce Super Block blocking buffer in PBS for 1-2 hr and then wash plates with wash buffer (PBS, 0.05% Tween-20). Blot plates on paper towels. Then add 50 μl/well of diluted Anti-Human IL-6 Monoclonal, Biotin-labeled antibody at 0.50 mg/ml. Make dilutions of IL-6 stock in media (30, 10, 3, 1, 0.3, 0 ng/ml). Add duplicate samples to top row of plate. Cover the plates and incubate for 2 hours at RT on shaker. Plates are washed with wash buffer and blotted on paper towels. Dilute EU-labeled Streptavidin 1:1000 in Assay buffer, and add 100 μl/well. Cover the plate and incubate 1 h at RT. Plates are again washed with wash buffer and blotted on paper towels. Add 100 μl/well of Enhancement Solution and shake for 5 minutes. Read the plate on the Wallac DELFIA Fluorometer. Readings from triplicate samples in each assay are tabulated and averaged.

[1119] A positive result in this assay suggests AoSMC cell proliferation and that the polypeptide of the present invention may be involved in dermal fibroblast proliferation

and/or smooth muscle cell proliferation. A positive result also suggests many potential uses of polypeptides, polynucleotides, agonists and/or antagonists of the polynucleotide/polypeptide of the present invention which gives a positive result. For example, inflammation and immune responses, wound healing, and angiogenesis, as detailed throughout this specification. Particularly, polypeptides of the present invention and polynucleotides of the present invention may be used in wound healing and dermal regeneration, as well as the promotion of vasculargenesis, both of the blood vessels and lymphatics. The growth of vessels can be used in the treatment of, for example, cardiovascular diseases. Additionally, antagonists of polypeptides and polynucleotides of the invention may be useful in treating diseases, disorders, and/or conditions which involve angiogenesis by acting as an anti-vascular (e.g., anti-angiogenesis). These diseases, disorders, and/or conditions are known in the art and/or are described herein, such as, for example, malignancies, solid tumors, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; artheroscleric plaques; ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, uvietis and Pterygia (abnormal blood vessel growth) of the eye; rheumatoid arthritis; psoriasis; delayed wound healing; endometriosis; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; Osler-Webber Syndrome; plaque neovascularization; telangiectasia; hemophiliac joints; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and atherosclerosis. Moreover, antagonists of polypeptides and polynucleotides of the invention may be useful in treating anti-hyperproliferative diseases and/or anti-inflammatory known in the art and/or described herein.

[1120] One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

Example 43: Cellular Adhesion Molecule (CAM) Expression on Endothelial Cells

[1121] The recruitment of lymphocytes to areas of inflammation and angiogenesis involves specific receptor-ligand interactions between cell surface adhesion molecules (CAMs) on lymphocytes and the vascular endothelium. The adhesion process, in both normal and pathological settings, follows a multi-step cascade that involves intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial leukocyte adhesion molecule-1 (E-selectin) expression on endothelial cells (EC). The expression of these molecules and others on the vascular endothelium determines the efficiency with which leukocytes may adhere to the local vasculature and extravasate into the local tissue during the development of an inflammatory response. The local concentration of cytokines and growth factor participate in the modulation of the expression of these CAMs.

[1122] Briefly, endothelial cells (e.g., Human Umbilical Vein Endothelial cells (HUVECs)) are grown in a standard 96 well plate to confluence, growth medium is removed from the cells and replaced with 100 μl of 199 Medium (10% fetal bovine serum (FBS)). Samples for testing and positive or negative controls are added to the plate in triplicate (in 10 μl volumes). Plates are then incubated at 37°C for either 5 h (selectin and integrin expression) or 24 h (integrin expression only). Plates are aspirated to remove medium and 100 μl of 0.1% paraformaldehyde-PBS(with Ca++ and Mg++) is added to each well. Plates are held at 4°C for 30 min. Fixative is removed from the wells and wells are washed 1X with PBS(+Ca,Mg) + 0.5% BSA and drained. 10 μl of diluted primary antibody is added to the test and control wells. Anti-ICAM-1-Biotin, Anti-VCAM-1-Biotin and Anti-E-selectin-Biotin are used at a concentration of 10 μg/ml (1:10 dilution of 0.1 mg/ml stock antibody). Cells are incubated at 37°C for 30 min. in a humidified environment. Wells are washed three times with PBS(+Ca,Mg) + 0.5% BSA. 20 μl of diluted ExtrAvidin-Alkaline Phosphotase (1:5,000 dilution, refered to herein as the working dilution) are added to each well and incubated at 37°C for 30 min. Wells are washed three times with PBS(+Ca,Mg)+0.5% BSA. Dissolve 1 tablet of p-Nitrophenol Phosphate pNPP per 5 ml of glycine buffer (pH 10.4). 100 μl of pNPP substrate in glycine buffer is added to each test well. Standard wells in triplicate are prepared from the working dilution of the ExtrAvidin-Alkaline Phosphotase in glycine buffer: 1:5,000 (10^{0}) > $10^{-0.5}$ > 10^{-1} > $10^{-1 5}$. 5 μl of each dilution is added to triplicate wells and the resulting AP

content in each well is 5.50 ng, 1.74 ng, 0.55 ng, 0.18 ng. 100 μl of pNNP reagent is then added to each of the standard wells. The plate is incubated at 37°C for 4h. A volume of 50 μl of 3M NaOH is added to all wells. The plate is read on a plate reader at 405 nm using the background subtraction option on blank wells filled with glycine buffer only. Additionally, the template is set up to indicate the concentration of AP-conjugate in each standard well [5.50 ng; 1.74 ng; 0.55 ng; 0.18 ng]. Results are indicated as amount of bound AP-conjugate in each sample.

Example 44: Alamar Blue Endothelial Cells Proliferation Assay

[1123] This assay may be used to quantitatively determine protein mediated inhibition of bFGF-induced proliferation of Bovine Lymphatic Endothelial Cells (LECs), Bovine Aortic Endothelial Cells (BAECs) or Human Microvascular Uterine Myometrial Cells (UTMECs). This assay incorporates a fluorometric growth indicator based on detection of metabolic activity. A standard Alamar Blue Proliferation Assay is prepared in EGM-2MV with 10 ng /ml of bFGF added as a source of endothelial cell stimulation. This assay may be used with a variety of endothelial cells with slight changes in growth medium and cell concentration. Dilutions of the protein batches to be tested are diluted as appropriate. Serum-free medium (GIBCO SFM) without bFGF is used as a non-stimulated control and Angiostatin or TSP-1 are included as a known inhibitory controls.

[1124] Briefly, LEC, BAECs or UTMECs are seeded in growth media at a density of 5000 to 2000 cells/well in a 96 well plate and placed at 37-C overnight. After the overnight incubation of the cells, the growth media is removed and replaced with GIBCO EC-SFM. The cells are treated with the appropriate dilutions of the protein of interest or control protein sample(s) (prepared in SFM) in triplicate wells with additional bFGF to a concentration of 10 ng/ ml. Once the cells have been treated with the samples, the plate(s) is/are placed back in the 37° C incubator for three days. After three days 10 ml of stock alamar blue (Biosource Cat# DAL1100) is added to each well and the plate(s) is/are placed back in the 37°C incubator for four hours. The plate(s) are then read at 530nm excitation and 590nm emission using the CytoFluor fluorescence reader. Direct output is recorded in relative fluorescence units.

[1125] Alamar blue is an oxidation-reduction indicator that both fluoresces and

changes color in response to chemical reduction of growth medium resulting from cell growth. As cells grow in culture, innate metabolic activity results in a chemical reduction of the immediate surrounding environment. Reduction related to growth causes the indicator to change from oxidized (non-fluorescent blue) form to reduced (fluorescent red) form. i.e. stimulated proliferation will produce a stronger signal and inhibited proliferation will produce a weaker signal and the total signal is proportional to the total number of cells as well as their metabolic activity. The background level of activity is observed with the starvation medium alone. This is compared to the output observed from the positive control samples (bFGF in growth medium) and protein dilutions.

Example 45: Detection of Inhibition of a Mixed Lymphocyte Reaction

[1126] This assay can be used to detect and evaluate inhibition of a Mixed Lymphocyte Reaction (MLR) by gene products (e.g., isolated polypeptides). Inhibition of a MLR may be due to a direct effect on cell proliferation and viability, modulation of costimulatory molecules on interacting cells, modulation of adhesiveness between lymphocytes and accessory cells, or modulation of cytokine production by accessory cells. Multiple cells may be targeted by these polypeptides since the peripheral blood mononuclear fraction used in this assay includes T, B and natural killer lymphocytes, as well as monocytes and dendritic cells.

[1127] Polypeptides of interest found to inhibit the MLR may find application in diseases associated with lymphocyte and monocyte activation or proliferation. These include, but are not limited to, diseases such as asthma, arthritis, diabetes, inflammatory skin conditions, psoriasis, eczema, systemic lupus erythematosus, multiple sclerosis, glomerulonephritis, inflammatory bowel disease, crohn's disease, ulcerative colitis, arteriosclerosis, cirrhosis, graft vs. host disease, host vs. graft disease, hepatitis, leukemia and lymphoma.

[1128] Briefly, PBMCs from human donors are purified by density gradient centrifugation using Lymphocyte Separation Medium (LSM®, density 1.0770 g/ml, Organon Teknika Corporation, West Chester, PA). PBMCs from two donors are adjusted to 2 x 10^6 cells/ml in RPMI-1640 (Life Technologies, Grand Island, NY) supplemented with 10% FCS and 2 mM glutamine. PBMCs from a third donor is adjusted to 2 x 10^5

cells/ml. Fifty microliters of PBMCs from each donor is added to wells of a 96-well round bottom microtiter plate. Dilutions of test materials (50 μl) is added in triplicate to microtiter wells. Test samples (of the protein of interest) are added for final dilution of 1:4; rhuIL-2 (R&D Systems, Minneapolis, MN, catalog number 202-IL) is added to a final concentration of 1 μg/ml; anti-CD4 mAb (R&D Systems, clone 34930.11, catalog number MAB379) is added to a final concentration of 10 μg/ml. Cells are cultured for 7-8 days at 37°C in 5% CO_2, and 1 μC of [^{3}H] thymidine is added to wells for the last 16 hrs of culture. Cells are harvested and thymidine incorporation determined using a Packard TopCount. Data is expressed as the mean and standard deviation of triplicate determinations.

[1129] Samples of the protein of interest are screened in separate experiments and compared to the negative control treatment, anti-CD4 mAb, which inhibits proliferation of lymphocytes and the positive control treatment, IL-2 (either as recombinant material or supernatant), which enhances proliferation of lymphocytes.

[1130] One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

[1131] It will be clear that the invention may be practiced otherwise than as particularly described in the foregoing description and examples. Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

[1132] The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, laboratory manuals, books, or other disclosures) in the Background of the Invention, Detailed Description, and Examples is hereby incorporated herein by reference. Further, the paper copy on CD-ROM of the sequence listing submitted herewith and the corresponding computer readable form on CD-ROM are both incorporated herein by reference in their entireties. Moreover, the hard copy of and the corresponding computer readable form of the Sequence Listing of Serial No. 60/124,270 and International Application No. PCT/US00/05988 are also incorporated herein by reference in their entireties.